PB86-118098

Drinking Water Criteria Document for Selenium (Final Draft)

Life Systems, Inc., Cleveland, OH

Prepared for

Environmental Protection Agency, Washington, DC

Apr 85

U.S. Department of Commerce
National Technical Information Service
NTIS

PB86-118098

DRAFT
DO NOT CITE OR QUOTE

TR-540-64B

FINAL DRAFT FOR THE DRINKING WATER CRITERIA DOCUMENT ON SELENIUM

April 1985

Prepared Under Contract 68-01-6750

by

ICAIR
LIFE SYSTEMS, INC.
Cleveland, OH 44122

for

Health Effects Branch
Criteria and Standards Division
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC 20460

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

DISCLAIMER

This document is a preliminary draft. It has not been released formally by the Office of Drinking Water, U.S. Environmental Protection Agency, and should not at this stage be construed to represent Agency policy. It is being circulated for comments on its technical content.

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

	2.	3. RECIPIENT'S ACCESSION NO. PB86 118098/AS
SUBTITLE Drinking Water Criteria Document for Selenium		5. REPORT DATE 4/85 6. PERFORMING ORGANIZATION CODE
HOR(S) Environmental Protection Agency		8. PERFORMING ORGANIZATION REPORT NO.
PERFORMING ORGANIZATION NAME AND ADDRESS Same as box 12.		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS U.S. Environmental Protection Agency Office of Drinking Water (WH-550) 401 M St., S.W., Washington, D.C. 20460		13. TYPE OF REPORT AND PERIOD COVERED Scientific review 14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on selenium. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of selenium
- Toxicokinetics and human exposure to selenium
- Health Effects of selenium in humans and animals
- Mechanisms of toxicity of selenium
- Quantification of toxicological effects of selenium

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Selenium properties Selenium exposure Selenium toxicity Drinking Water		

18. DISTRIBUTION STATEMENT OPEN	19. SECURITY CLASS *(This Report)* Non-sensitive	21. NO. OF PAGES 189
	20. SECURITY CLASS *(This page)* Non-sensitive	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

TABLE OF CONTENTS

PAGE

LIST OF FIGURES iv

LIST OF TABLES iv

I. SUMMARY I-1

II. GENERAL INFORMATION AND PROPERTIES II-1

- A. Physical and Chemical Properties II-1
- B. Manufacture and Uses II-2
- C. Extent and Significance of Problems II-2
    - 1. Natural II-3
    - 2. Industrial II-6
- D. Summary II-6

III. TOXICOKINETICS III-1

- A. Absorption III-1
- B. Tissue Distribution III-2
- C. Metabolism III-5
- D. Excretion III-9
- E. Summary III-13

IV. HUMAN EXPOSURE IV-1

- A. Exposure Estimation IV-1
    - 1. Drinking Water IV-2
    - 2. Diet IV-2
    - 3. Air IV-4
- B. Summary IV-4

V. HEALTH EFFECTS IN ANIMALS V-1

- A. Animal Nutritional Requirements V-1
- B. Acute Toxicity V-4
    - 1. Livestock V-4
    - 2. Laboratory Animals V-6
- C. Chronic Toxicity V-9
    - 1. Livestock V-9
    - 2. Laboratory Animals V-10

continued-

Table of Contents - continued

PAGE

- D. Synergism/Antagonism . . . V-15
- E. Teratogenicity . . . V-20
- F. Mutagenicity . . . V-39
- G. Carcinogenicity and Anticarcinogenicity . . . V-44
    - 1. Carcinogenicity . . . V-44
    - 2. Anticarcinogenicity . . . V-61
- H. Summary . . . V-69

VI. HEALTH EFFECTS IN HUMANS . . . VI-1

- A. Human Nutritional Requirements . . . VI-1
- B. Acute Toxicity . . . VI-4
- C. Chronic Toxicity . . . VI-7
- D. Teratogenicity . . . VI-12
- E. Mutagenicity . . . VI-15
- F. Carcinogenicity . . . VI-20
- G. Epidemiology Studies . . . VI-22
    - 1. Cardiovascular . . . VI-22
    - 2. Relationship to Cancer . . . VI-23
    - 3. Industrial and Community Studies . . . VI-26
    - 4. Miscellaneous Studies . . . VI-28
- H. Summary . . . VI-29

VII. MECHANISMS OF TOXICITY . . . VII-1

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS . . . VIII-1

- A. Non-Carcinogenic Effects . . . VIII-5
    - 1. Toxic Effects . . . VIII-5
    - 2. Nutritional Requirements . . . VIII-9
- B. Quantification of Non-Carcinogenic Effects . . . VIII-11
    - 1. One-Day Health Advisory . . . VIII-11
    - 2. Ten-Day Health Advisory . . . VIII-13
    - 3. Adjusted Acceptable Daily Intake . . . VIII-15
- C. Carcinogenic Effects . . . VIII-19
- D. Anticarcinogenic Effects . . . VIII-21
- E. Quantification of Carcinogenic Effects . . . VIII-22
- F. Existing Guidelines and Standards . . . VIII-23
- G. Special Considerations . . . VIII-24

continued-

Table of Contents - continued

PAGE

1. High Risk Populations VIII-24
2. Interactions VIII-24
3. Beneficial Effects VIII-25

H. Summary VIII-25

IX. REFERENCES IX-1

LIST OF FIGURES

FIGURE PAGE

II-1 Regional Distribution of Forages and Grains Which are Low, Variable and Toxic in Selenium II-5

LIST OF TABLES

TABLE

II-1 Selenium in Various Geological Materials II-4
III-1 Selenium Excretion in the Rat III-11
IV-1 Reported Daily Dietary Intake of Selenium IV-3
V-1 Selenium Dietary Requirements in Livestock V-2
V-2 Acute Selenium Toxicity in Livestock V-5
V-3 Acute Toxicity of Selenium in Rats V-7
V-4 Acute Toxicity of Selenium in Rabbits V-8
V-5 Chronic Toxicity of Selenium in Livestock V-11
V-6 Chronic Toxicity of Selenium in Laboratory Animals V-12
V-7 Teratology in Animals Chronically Exposed to Selenium V-21
V-8 Selenium Transfer from Mother to Egg or to Mammalian Fetus Across the Placenta V-31
V-9 Teratology Influenced by Selenium Interactions with Other Chemicals V-36
V-10 Distribution of Neoplasms in Rats on Experimental Diets . . . V-48
V-11 Summary of Experimental Results on Selenium Carcinogenesis . V-52
V-12 Tumors in Rats Fed a Selenate-Supplemented Diet V-57
VI-1 Safe and Adequate Ranges of Daily Selenium Intake VI-5
VI-2 Symptoms and Signs of Selenium Toxicity VI-9
VI-3 Selenium Content in Human Tissues (Necropsy Data) VI-10
VI-4 Selenium Concentrations in Whole Blood from 19 Collection Sites in the United States VI-11
VIII-1 Recommended Estimated Adequate and Safe Intakes VIII-12
VIII-2 Summary of Quantification of Toxicological Effects VIII-26

I. SUMMARY

The metalloid selenium, discovered in 1817 by John Jakob Berzelius, is an element with the atomic number 34 and atomic weight of 78.96. It belongs to the same group of elements as sulfur, and is usually found as a contaminant in sulfur deposits. The "metallic" form is silver-gray, but it can be ground into a coarse black powder or an extremely fine red powder. It is ubiquitous in rocks and soils throughout the world. In the United States, the most deficient regions are the Northwest, Northeast, Southeast and areas of the Midwest, particularly those states adjoining the Great Lakes. The Plains States and the Southwest generally have higher concentrations of selenium in soils. The largest known selenium deposit in the world is in Noranda, Quebec, Canada. Selenium forms a wide range of compounds, some of which are volatile (SeO_3, H_2Se) and others nonvolatile such as organic selenium compounds (selenomethionine, selenocysteine, selenocystine).

Selenium is a by-product of copper mining and smelting and sulfur purification. It is also found in high concentration in soft coal; a principal source of selenium in the atmosphere is thus from the burning of coal. Atmospheric selenium enters the water supply and soil, since virtually 100% of particulate selenium is removed from the air by condensation of water vapor. Selenium is used as a constituent of a variety of components in the electronic, photographic, xerographic, glass and paint industries.

While selenium may find its way into water through a variety of routes, the selenium content of water is largely dependent upon its content in aquifers and soils. The local soil concentration appears to correlate well with animal and human serum concentrations of selenium.

Bioconcentration by plants occurs through the uptake of selenium from soil and water. Selenium does not appear to constitute an essential element for plant growth, but many studies indicate that normal animal growth and reproduction are dependent upon selenium. There is increasing evidence from studies in low selenium areas and attempts at total parenteral nutrition that selenium is an essential trace element for humans.

Exposure of the general public to selenium appears to be very low, but there are specific problems which may arise from exposure to naturally occurring selenium or selenium which is a by-product of manufacturing processes. Human absorption of selenium may occur through the mucous membranes when exposed to fumes, from the gastrointestinal (G.I.) tract by ingestion of water or food and potentially through the skin by direct application. According to animal and human studies, the majority of selenium taken into the body is absorbed from the G.I. tract. Over 40% of the ingested selenium is excreted in the urine. Virtually all of the remainder is excreted in the feces. Thus, accumulation of selenium in tissues is directly related to its daily intake. Selenium functions as a lipid antioxidant in conjunction with vitamin E. Selenium aids in the transport of vitamin E, potentiates its action and stimulates its storage. Selenium is incorporated into enzymes that regulate body processes, with glutathione peroxidase being perhaps the most important. There is evidence that this selenium-containing enzyme may act to prevent chemical damage to important biomembranes. Glutathione peroxidase may also function in the pentose phosphate shunt, and therefore be of some importance to the metabolism of red blood cells in all mammalian species.

The principal routes of selenium exposure in humans are drinking water, food and air. Water concentrations of selenium are generally 5 µg/L or less; however, approximately 250,000 people in the U.S. on public water systems are supplied with water containing more than 10 µg/L. Selenium intake from food ranges from 100 to 200 µg/day for adults. Intake of selenium from air is less than 1 µg/day. There are insufficient data to determine the relative contribution of the three sources to total intake. Available information indicates that food is the predominant source of selenium for most individuals.

Both selenium toxicity and deficiency has been clearly documented in animals. A muscle disorder found in lambs and calves known as "white muscle disease," is related to selenium deficiency. There are several recognizable forms of selenium intoxication. Excess selenium produces an acute syndrome in range animals known as "blind staggers." A chronic form of toxicity known as "alkali disease" is also found in animals inhabiting seleniferous areas. There is mounting evidence that selenium may be anticarcinogenic in some species, and there is anecdotal evidence that it protects against the incidence of cancer in humans. There appears to be reasonably firm evidence of teratogenicity in egg-laying species, including chickens and aquatic forms, and also in the laboratory rat and mouse. Mutagenesis has been documented with selenium compounds in bacterial and in vitro cell culture systems. Teratogenicity in humans remains a possibility; however, the only evidence of abnormality of the human fetus appears to rest on rather poorly documented and anecdotal reports.

There have been industrial accidents involving selenium which resulted in acute human intoxication producing signs of skin and/or mucous membrane irritation and some gastrointestinal symptoms. Documentation of selenium's chronic toxicity in humans is less clear than for other animals. In high-selenium areas or in industrial situations where there is increased selenium exposure, there have been cases of elevated selenium blood levels associated with symptoms ranging from vague malaise, pallor, fatigue and gastrointestinal symptoms to a variety of skin, hair, tooth and nail lesions; however, levels that produce symptomatology are ill-defined. The relationship of selenium to human cancer induction or prevention has been discussed and remains equivocal.

No suitable studies were located that could serve as the basis for calculation of a one-day Health Advisory (HA) in children or adults. Ten-day HA values (described below) were taken to be conservative estimates of appropriate one-day HA values. The no-observed-adverse-effect level (NOAEL) of 0.41 mg Se/kg/day, from a six-week duration feeding study in rats, was employed to calculate the ten-day HA values of 0.041 mg/L (41 µg/L) for the 10-kg child and 0.144 mg/L (144 µg/L) for the 70-kg adult. The lowest-observed-adverse- effect level (LOAEL) of 3.20 mg/day, based upon the minimum daily selenium intake reported in a study of humans with chronic selenosis, was used to calculate an ADI of 0.213 mg/day (213 µg/day) and an AADI of 0.106 mg/L (106 µg/L).

The U.S. Environmental Protection Agency's (USEPA) maximum contaminant level (MCL) for selenium in drinking water is 10 µg/L. An action level of 10 µg/L is recommended by the World Health Organization (WHO). The USEPA's ambient water quality criterion is 10 µg/L.

Excess carcinogenic risk values for naturally occurring selenium (selenite or selenate) compounds have not been calculated since there was insufficient evidence of any carcinogenic effects in animals or humans.

The developing fetus was considered at increased risk to excess selenium exposure since studies in certain species of animals demonstrate tetratogenic effects at high doses. Selenium is antagonistic to toxic effects of silver, arsenic, cadmium and mercury.

II. GENERAL INFORMATION AND PROPERTIES

A. Physical and Chemical Properties

Selenium (symbol Se, atomic number 34, atomic weight 78.96) is found in nature, usually in the presence of sulfide-type ores of the heavy metals. Small quantities are also found in pyrite and minerals such as clausthalite, naumannite and tiemannite. Selenium exists in several allotropic forms: amorphous, with a density of 4.28; crystalline or red, with a density of 4.46 and a melting point below 200°C; and gray or metalloid, with a density of 4.81 and a melting point of 217°C. The crystalline form is metastable and changes into the stable metalloid form upon heating (Windholz 1976). Selenium may assume four oxidation states (-2, 0, +4, +6), and forms chemical compounds corresponding to those of sulfur. Heavy metal selenides (-2) are insoluble, and hydrogen selenide is a highly reactive gas that decomposes quickly in the presence of oxygen. The elemental form (0) is insoluble and is not rapidly oxidized or reduced in nature and thus becomes a major sink for selenium. The inorganic selenites (+4) combine with iron and aluminum sesquioxides (Fe_2O_3, Al_2O_3), forming stable absorption complexes (NAS 1976). Acid and reducing conditions reduce the inorganic selenites to elemental selenium. Alkaline and oxidizing conditions favor the formation and stability of the selenates (+6) which are readily soluble in water (Gissel-Nielsen 1977). Inorganic selenium may be converted to organic forms by biological activity (Chau et al. 1976).

B. Manufacture and Uses

Even though selenium is widely distributed in nature, the very small amount concentrated in any one area does not permit the mining of selenium alone. The majority of selenium used in the U.S. is produced from copper refinery slimes. Most U.S. selenium scrap is reprocessed in Canada and exported back to the U.S. markets (USBM 1980).

Selenium is used in the manufacture of photographic photocells and exposure meters as well as solar cells. It is also finding wide usage in electronic and solid-state applications. Selenium is used in xerography for copying printed materials, and it is used in the glass industry to decolorize glass and make ruby-colored glass and enamels (Weast and Astle 1979). It is also used as a pigment in the manufacture of paints and dyes (Wilber 1980).

The total quantity of selenium used in the United States in 1979 was approximately 818 thousand pounds. In 1978 and 1979, usage listed by end-product category was as follows: electronic and photocopier components, 35%; glass manufacturing, 30%; chemicals and pigments, 25%; and other, 10% (USBM 1980).

C. Extent and Significance of Problems

Selenium appearing in water supplies is of either industrial (man-made) or natural (soil and rock formation) origin. Selenium from these two major sources can enter drinking water supplies by the following routes: (1) the atmosphere, (2) leaching to ground water, or (3) runoff (Wilber 1980).

1. Natural

The selenium levels in various geological materials are given in Table II-1. The concentrations of total selenium in the western and southeastern regions are low compared to high concentrations which are prevalent in the west central region and the central part of the Gulf of Mexico coast. Figure II-1 demonstrates the regional distribution of selenium in forages and grains throughout the United States. The northwest, northeast and southeast regions produce grains and forages that contain low selenium concentrations.

The aqueous solubility of selenium compounds is the primary determinant of their transfer from soil and rocks to water supplies. Since selenates have the greatest water solubility, they are the most likely form of selenium to enter the water. Selenium can reach elevated levels in groundwater that has passed through seleniferous shales which contain high levels of soluble selenium (Tsongas and Ferguson 1977). The elevated levels of selenium in the groundwater obtained from seleniferous geological areas appear to be the only direct evidence that natural sources of selenium lead to high levels of this element in drinking water supplies. The NAS (1976) literature review indicated that irrigation drainage from seleniferous soils may potentially cause increased selenium levels in rivers and lakes.

Table II-1. Selenium in Various Geological Materials.

Material	Selenium, μg/g	Reference
Oil shales	1-5	Chappell (1979)
Shales	0.6	Kolm (1975)
Other rock types (sandstone, igneous rocks, limestone)	0.05	Kolm (1975)
Seawater	0.00009	Wilber (1980)
Soils (seleniferous)	4.5	Greathouse (undated)
Soils (non-seleniferous)	0.5	Greathouse (undated)

Reproduced from
best available copy.

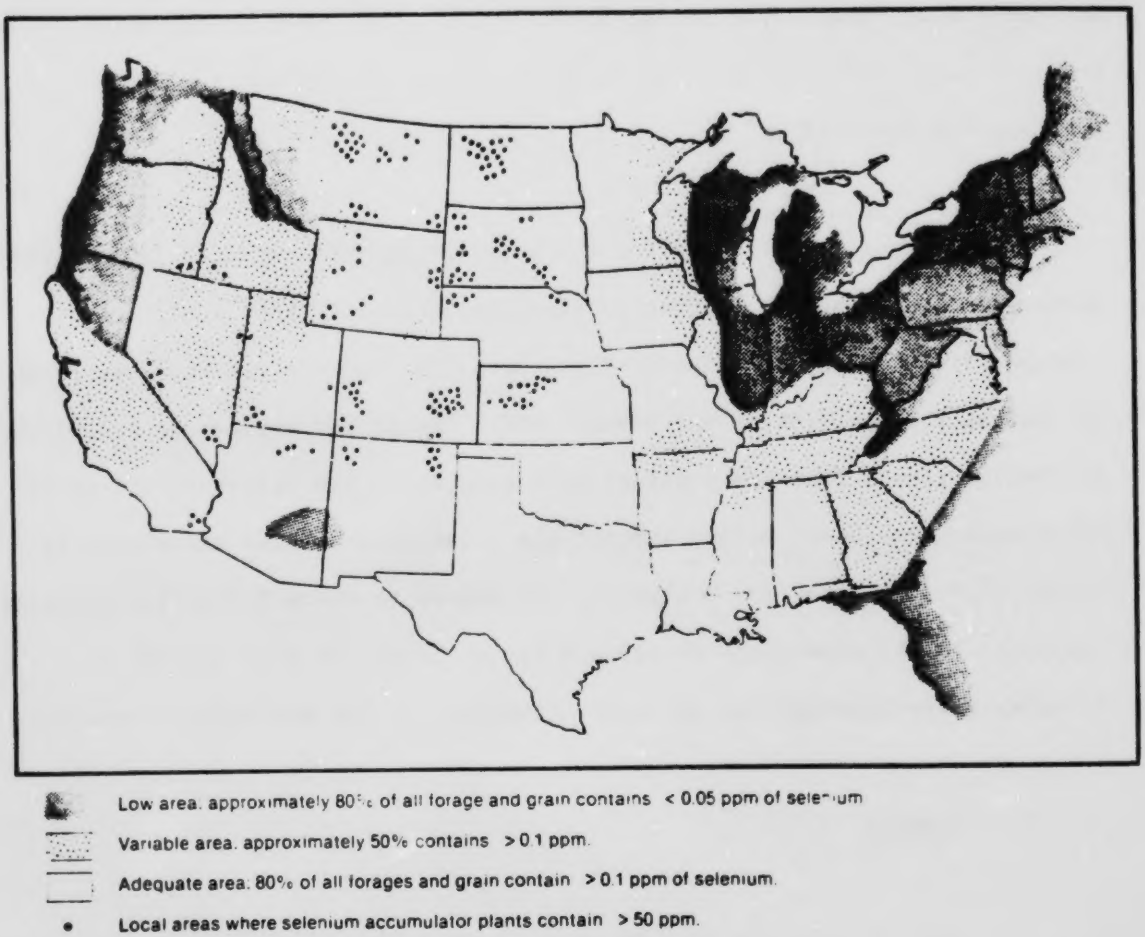
▨ Low area: approximately 80% of all forage and grain contains < 0.05 ppm of selenium
▨ Variable area: approximately 50% contains > 0.1 ppm.
☐ Adequate area: 80% of all forages and grain contain > 0.1 ppm of selenium.
● Local areas where selenium accumulator plants contain > 50 ppm.

Figure II-1 Regional Distribution of Forages and Grains which are Low, Variable and Toxic in Selenium. From Ammerman (1981) and Kubota and Allaway (1972)

2. Industrial

The two major sources of industrial selenium emissions are coal combustion and nonferrous mining operations (Scott 1976). Other sources include: precious metal refinery operations, glass manufacturing, and fuel oil combustion (USBM 1980).

During fossil fuel combustion the selenium dioxide produced is reduced by excess amounts of sulfur dioxide to elemental selenium (NAS 1976). Atmospheric emissions from fossil fuel combustion contain elemental selenium in the vapor phase (Zoller and Reamer 1976). Metal refineries and fossil fuel combustion plants that are equipped with electronic precipitators and other air-cleaning equipment reduce atmospheric selenium emissions significantly (Scott 1976). Information indicating the degree to which industrial selenium emissions to the atmosphere contribute to the levels of this element in drinking water supplies has not been documented in the available literature.

D. Summary

The entry of selenium into drinking water relates primarily to the aqueous solubility of the particular selenium compound and the proximity of the drinking water supply to the source of selenium. Since most water-soluble selenium compounds occur as natural selenates, natural sources of selenium will make up the largest contribution to drinking water sources.

Industrial air-cleaning equipment significantly reduces selenium emissions to the atmosphere. The industrial selenium waste not removed by this equipment may enter water supplies via precipitation washout or runoff but is largely restricted to the immediate vicinity of metal refineries and fossil fuel combustion sites.

III. TOXICOKINETICS

A. Absorption

Selenium can enter the body by ingestion and inhalation routes. There is less well documented evidence regarding entry to the body by skin absorption.

Animal studies indicate that ingested selenium is well absorbed from the gastrointestinal tract. Studies by Thomson and Stewart (1973) of gastrointestinal absorption rates of ^{75}Se-selenite and ^{75}Se-selenomethionine in female Wistar rats yielded estimates of greater than 90% absorption. In these studies, two groups of 20 rats each received a dose of approximately 5 μCi ^{75}Se-selenomethionine (approximately 5 μg Se), one by intravenous (i.v.) injection, and the other by intragastric intubation. Two additional groups of 20 rats were given i.v. or oral doses of ^{75}Se-selenite containing not more than 5 μg Se. The three methods used to estimate intestinal absorption yielded percentages ranging from 91 to 93 for selenite and from 95 to 97 for selenomethionine.

In an additional study (Thomson et al. 1975), intestinal absorption of selenocystine and selenomethionine was measured in two groups of 25 female Wistar rats. Approximately 5 μCi of ^{75}Se-selenocystine and approximately 2 μCi of ^{75}Se-selenomethionine were given by gastric intubation. Each dose contained not more than 5 μg Se. The authors estimated that 81.1% of the ^{75}Se-selenocystine and 86.4% of the ^{75}Se-selenomethionine were absorbed.

There are only a few studies on selenium absorption in humans. Thomson and Stewart (1974) measured gastrointestinal absorption in three women, 20, 25 and 33 years of age. The mean height was 1.60 m and the mean weight was 57 kg. Under conditions of fasting, a measured oral dose of approximately 10 μCi ^{75}Se-selenite containing not more than 10 μg Se was given to each. The intestinal absorptions calculated for each of the three women were 70%, 64%, and 44% of the administered dose, respectively.

There is little quantitative information available on the absorption of selenium through the lungs as a gas or as finely dispersed particles. There is also a lack of quantitative information on the absorption of selenium through the skin, although toxicity has been reported by both routes (see below). However, Cummins and Kimura (1971) described an unpublished study showing no apparent skin absorption from 1% selenium sulfide in shampoo used for one year.

B. Tissue Distribution

Whole blood selenium by itself is not an accurate indicator of selenium body burden. The amounts of selenium in other tissues, such as hair and urine, in combination with blood levels provide information to best estimate selenium body burdens (Burk 1976, Stewart et al. 1978).

Humans receiving 50 to 125 μg/L of selenium via drinking water have a mean urine concentration of 77 μg/L (range: 10 to 231 μg/L). Individuals drinking water containing only 17 μg/L Se had much less selenium in the urine. Regardless of intake, males excreted more urinary selenium than did females (Tsongas and Ferguson 1978).

Shearer and Hadjimarkos (1975) studied the selenium content of human milk in different geographical regions of the United States. The mean selenium concentration in human milk was found to be 18 μg/L (range: 7 to 33 μg/L). They reported high selenium concentrations in human milk in the West, low concentrations in the Northwest and Northeast, and variable concentrations in other regions of the country. They concluded that the selenium concentration of human milk was a function of food concentration.

In investigations to determine the distribution of selenium in domestic farm animals, Dudley (1936) fed sodium selenite or selenium-containing plants to several species. They fed selenium to a hog, a calf, and a sheep at levels of 19.64 mg/kg, 20 mg/kg, and 11.21 mg/kg, respectively, produced a fatal outcome within a range from six hours (calf) to three days (hog). The blood levels of selenium were: 5 μg/mL (hog); 7 μg/mL (sheep) and 27 μg/mL (calf). The highest selenium levels were found in the liver, kidney, and spleen. Lesser concentrations were found in the heart, lungs, brain, and muscle of the three species.

In a study of four sheep on selenium-deficient diets and four with adequate selenium intake, Handreck and Godwin (1970) introduced a ^{75}Se-labeled pellet (1.0 g elemental selenium as sodium selenite with 0.25 mCi activity) into the rumen of each sheep and monitored them in metabolism cages for a period of one month prior to sacrifice. Selenium was detected in each tissue examined, with the highest levels being present in kidney, liver, and various glandular tissues (pancreas, pituitary, pineal). The fat, bile, marrow, and parts of the eye had the lowest levels of selenium. Interestingly, the initial selenium status (deficient diet or adequate diet) of the animals had little effect on the resulting overall distribution.

Kincaid et al. (1977) studied selenium distribution in three groups of five male Holstein calves fed a diet containing 0.3 μg/g Se supplemented with 0, 0.1, or 1.0 μg/g added selenium, as sodium selenite. Their study showed that the effect of supplemental dietary selenium on tissue uptake of ^{75}Se is generally reflected by the blood. At the beginning of the study, the calves were approximately 120 days of age and averaged 105 kg in weight. After 28 days on the experimental diets, they were orally dosed with 608 μCi ^{75}Se (specific activity 93 mCi/mg selenium) contained in gelatin tablets. They were sacrificed 48 hours after dosing. Blood ^{75}Se concentrations were reduced about 15% and 35% with 0.1 μg/g and 1.0 μg/g added dietary selenium, respectively. The kidney, middle and lower small intestine, cecum, and liver contained the greatest amounts of ^{75}Se in each group.

It appears that the primary tissue sites for selenium deposition, in decreasing concentrations, are the kidney, liver, spleen and middle and lower segments of the small intestine, with the heart, lungs and brain containing lesser concentrations (Kincaid et al. 1977).

C. Metabolism

Selenium functions as a lipid antioxidant in concert with vitamin E. Selenium competes with sulfur in the biochemical pathways and acts as an antioxidant of the sulfur-containing essential amino acids, cystine and methionine (Burk 1978, Underwood 1977).

Selenium is incorporated into enzymes that regulate normal body processes. Perhaps the most important is glutathione peroxidase, but it is also required for coenzyme A. Glutathione peroxidase protects cellular and subcellular membranes from peroxidative damage by inhibition and destruction of peroxides, then by reducing the amount of vitamin E necessary to maintain integrity of these membranes (Scott 1979).

Selenium also functions as a catalyst in many biological processes. Selenium in conjunction with vitamin E protects cell membranes and organelles from oxidative damage as well as potentiates transfer of ions across cell membranes. Selenium assists protein synthesis in erythrocytes and liver organelles and aids in the retention of vitamin E in blood plasma (Scott 1979). Selenium also augments the immune response and has a role in inflamation. Neutrophils, peritoneal macrophages and pulmonary alveolar macrophages from selenium-deficient animals have low amounts of glutathione peroxidase activity and decreased microcidal activity (Serfass and Ganther 1975, Boyne and Arthur 1979). Further, the phagocytic capability of neutrophils was not diminished, but the ability of the cells to destroy the phagocytized material was compromised (Boyne and Arthur 1979). Selenium has also been reported to enhance antibody synthesis, thereby amplifying the immune system in response to antigenic stimulation (Desowitz and Barnwell 1980, Koller et al. 1979, Spallholz et al. 1975). Selenium has also been reported to effect prostaglandin biosynthesis (Nugteren and Hazelhof 1973), regulation of carbohydrate metabolism (Eggleston and Krebs 1974) and the normal function of several other body processes (Burk 1978).

At concentrations of normally ingested selenium, the element is incorporated into functional proteins. At higher concentrations, selenium replaces sulfur in proteins and other molecules. One mechanism of selenium toxicity may be the instability this replacement causes in functional proteins (Stadtman 1974).

Microorganisms can activate selenium with adenosine triphosphate by the same mechanism used for sulfate ions (Wilson and Bandurski 1956). Although activated sulfates are reduced to sulfite by phosphosulfate, the analogous reduction of selenates to selenites and the intermediate formation of 3'-phosphoadenosine-5'-phosphoselenate has not been proven. Since reduction of activated sulfate is an important step in the detoxification of foreign compounds and steroid metabolism, it is conceivable that reduction of activated selenate and the formation of 3'-phosphoadenosine-5'-phosphoselenate could be significant (Lipmann 1958).

It has been shown that both selenate and selenite ions are incorporated into organic molecules as selenide, but the mechanism of this reduction has not been demonstrated (Stadtman 1974).

Mammalian tissues may partially detoxify selenite by methylation. Dimethylselenide is formed by mouse lung, liver and kidneys from selenite using S-adenosylmethionine and reduced glutathione. Thus, glutathione is essential during methylation and the probable donor of the methyl group is S-adenosyl-L-methionine. Mouse muscle, spleen and heart failed to show any evidence of methylation (Ganther 1966).

Both selenite and selenate are methylated to form trimethyl selenonium ion. This is the principle excretory product of selenium in the urine with 30% to 50% of urinary selenium in this form (Byard 1968, Palmer et al. 1969, Palmer and Olson 1974). As in the case of dimethylselenide, the trimethylselenonium ions are less toxic than either selenite or selenate ions (Obermeyer et al. 1971).

Methylated metabolite ions are less toxic themselves but may increase the toxicity of other materials. Dimethylselenide increases the toxicity of mercury (Parizek et al. 1971a) and trimethylselenonium increases the toxicity of arsenic (Obermeyer et al. 1971).

Sheep skeletal muscle contains a small selenoprotein (molecular weight of 10,000) which has been uncharacterized to date. Although the selenium appears to be an integral part of this protein, its position, its function and whether or not it is an essential element remain unknown (Pedersen et al. 1972).

Another important feature of selenium is reduction. Selenium can react with sulfhydryl groups of either proteins or thiols to form selenotrisulfide derivatives (Ganther 1968). These derivatives may react with glutathione to form selenopersulfide (Ganther 1971). Selenium, thus, is incorporated into the selenium-dependent enzyme glutathione peroxidase, an enzyme which catalyzes hydrogen peroxide reduction. Selenium-deficient animals have low glutathione peroxidase activity in red blood cells. This low activity is restored by selenium administration (Rotruck et al. 1973). This enzyme has a molecular weight of 84,000 and is composed of four equal subunits, each containing one selenium atom (Flohe et al. 1973).

Selenium functions via glutathione peroxidase as a lipid antioxidant and protects the body against lipid peroxidation. The primary role of this selenium-dependent enzyme is protection of cells against oxidant damage, along with other cellular antioxidant defense mechanisms such as vitamin E, catalase, and superoxide dismutase (Hoekstra 1975). The enzyme reduces several hydroperoxides as well as hydrogen peroxide (Sunde and Hoekstra 1980). Selenium in the form of selenocysteine appears to be the active principle in glutathione peroxidase (Forstrom et al. 1978).

D. Excretion

Rosenfeld (1964) investigated the effects of mode and frequency of selenium administration on urinary, fecal and respiratory excretion rates. The author studied male and female Sprague-Dawley rats weighing 300 to 450 g and 200 to 300 g, respectively. Following a single dose of 7.5 μg of ^{75}Se administered by a variety of routes, the percentage of administered dose of ^{75}Se excreted in 24 hours in the urine and feces, respectively, was: subcutaneous, 12.9% and 3.7%; intraperitoneal 26.0% and 4.0%; and intragastric, 34.7% and 12.5%. Repeated administration of tracer doses by various routes appeared to alter the total elimination pattern observed after a single dose, and the amounts excreted via the kidney, gut or lung show quantitative differences. The urinary tract was determined to be the primary site of elimination of injected tracer doses. It appears that in the rat, 40% of the injected dose is excreted in the urine, while another 50% or less is excreted by the gastrointestinal tract and lung (Rosenfeld 1964). Selenium was found in the urine, feces and expired air up to 150 days after its administration. After subcutaneous injections, respiratory elimination was not detected. Administration of repeated doses of 2.5 mg of selenium H_2SeO_3/kg mixed with ^{75}Se ($H_2{}^{75}SeO_3$) appeared to reverse the route of elimination, since urinary excretion decreased and excretion of ^{75}Se via the feces and the lung increased.

In Wistar rats exposed to ^{75}Se-selenocystine, ^{75}Se-selenomethionine, and ^{75}Se-selenite orally, Thomson and Stewart (1973) and Thomson et al. (1975)

determined urinary and fecal excretion rates. Female rats bred from the same colony, initially weighing 90 to 120 g, were divided into two groups of 12. They were maintained on tap water and a stock diet containing 180 g available protein and 0.025 mg Se/kg. One of the groups was anesthetized with 5 mg sodium pentobarbitone and given approximately 5 μCi of ^{75}Se-selenocystine by gastric intubation. Approximately 2 μCi of ^{75}Se-selenomethionine was given to the second group by the same route (Thomson et al. 1975). Additionally, two groups of 12 female rats (140 to 160 g) were exposed by the same procedures to 5 μCi ^{75}Se-selenomethione or ^{75}Se-selenite (Thomson and Stewart 1973). The total dose level for the four groups never contained more than 5 μg Se. Following dosing, the rats were maintained in metabolic cages and urine and feces were collected separately. Collections were completed at 24-hour intervals for seven days. Table III-1 summarizes the percentage of total dose administered that was excreted in the seven-day period by each group of animals. In these studies, the feces was the primary route of excretion.

Human excretion of selenium was studied by Waterlow et al. (1969) in eight male infants, aged 7 to 16 months, who had been hospitalized with severe malnutrition. All but one were on high-protein (3 to 5 g/kg/day) diets at the beginning of the study. The infants were given single doses of 0.1 μCi ^{75}Se-methionine, six orally and two intravenously. The 24-hour excretion distribution, reported for only one orally dosed infant, was 4.5% urinary and 8.1% fecal. The range of 48-hour excretion values were: 3.2% to 7.25% urinary and 3.6% to 15.15% fecal following oral administration, and 8.6% to 8.95% urinary and 1.7% to 2.95% fecal following intravenous administration. It appears that if

Table III-1. Selenium Excretion in the Rat.[a]

Dose	Excretion (% of total administered dose)	
	Urine	Feces
^{75}Se-Selenocystine (5 μCi)	11.4	27.1
^{75}Se-Selenomethionine (2 μCi)	5.0	22.2
^{75}Se-Selenomethionine (5 μCi)	4.2	15.6
^{75}Se-Sodium selenite (5 μCi)	12.7	20.6

[a] Adapted from Thomson and Stewart (1973), Thomson et al. (1975).

selenomethionine was administered by mouth, more radioactivity was excreted in the feces than in the urine during the first 48 hours. However, intravenously administered selenomethionine was excreted in the urine to a greater extent than in the feces. The loss in the feces tended to remain higher than that in the urine for about the first ten days in the orally dosed subjects. However, the fecal loss, expressed as percent of retained dose per day, declined as time went on, whereas the rate of loss in the urine remained rather constant. These findings are explained by differential absorption leading to differing blood levels, with resulting differences in the tubular load of selenium in the kidneys.

As described previously, Thomson and Stewart (1974) studied selenium metabolism in three women. An oral dose of approximately 10 μCi ^{75}Se-selenite, containing not more than 10 μg Se, was administered to the fasting women. A gelatin capsule containing 50 mg brilliant blue and 200 mg methyl cellulose was swallowed as a marker by each woman immediately after the ^{75}Se dose. During the initial 24 hours after the dose, urine was collected every hour for ten hours, then every two hours for six hours, and once again at the end of eight hours. Following this, 24-hour collections were made each day for 13 days. All individual stools for at least 14 days were collected separately. Thereafter, a single fecal sample was obtained each week, and the urine was collected on the same day from each subject. Expired air was collected in Douglas bags for 8- to 10-minute collection periods at regular time intervals during the first nine hours. Dermal loss was measured by analysis of underclothing. Urine and fecal excretion for the first two weeks varied from 7% to 14%, and 58% to 33%, respectively, of the dose administered. No radioactivity was detected in expired air, with the exception that, on day one, traces of ^{75}Se of less than 0.02% of the dose were found in the HNO_3 and mercuric chloride solutions through which expired air had been passed. None was detected on day two. Dermal excretion was not detected during the first, second, or third day by the method used.

It appears from these studies that the primary routes of excretion are in the urine and feces and that the distribution between the two depends on the route and level of the dose and the length of time after exposure.

In a subsequent study, Stewart et al. (1978) measured the selenium balance in four "normal" women in New Zealand. A mean balance of +0.3 μg selenium per day was observed during 14 days of study. This study suggests that little selenium is retained and little is lost by routes other than urine and feces. The mean whole body selenium content for the four women was 6.1 mg, less than half of the only other estimate of 13 to 20 mg for persons living in the United States (Schroeder et al. 1970). No specific biological half-time for selenium has been suggested owing to the difficulty of measuring it directly.

E. Summary

Animal studies indicate that selenium is well absorbed (approaching 100%) when ingested orally as selenite, selenocystine or selenomethionine. Quantitative inhalation and dermal absorption studies have not been performed.

The primary deposition sites for selenium in the body, in order of decreasing concentration, are the kidney, liver and spleen. Based on the work of Kincaid et al. (1977), it is apparent that tissue concentrations are dose-dependent. Blood, hair and human milk all contain selenium, but the element is excreted primarily in the urine and feces. Urine concentrations have correlated well with the amount of selenium in drinking water, though good correlation with hair concentration has also been noted. Blood selenium concentrations fluctuate with daily intake.

Selenite and selenate are metabolized to less toxic ions which are excreted most readily in the urine. Selenium appears to be an essential element for animals and humans. Selenium is incorporated into proteins for some metabolic processes such as oxidation-reduction. The selenium-dependent enzyme, glutathionine peroxidase, functions as a lipid antioxidant and protects the body against lipid peroxidation in concert with vitamin E.

The primary routes of selenium excretion are urine and feces. The distribution between these two routes depends upon the route of exposure (more fecal elimination occurs following oral administration), the level of exposure and the length of time after exposure.

IV. HUMAN EXPOSURE

Humans may be exposed to selenium in drinking water, food and air. Detailed information concerning the occurrence of and exposure to selenium in the environment is presented in another document entitled, "Occurrence of Selenium in Drinking Water, Food, and Air" (Letkiewicz et al. 1984). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

A. Exposure Estimation

This analysis is limited to drinking water, food and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to selenium from sources other than the three considered here. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works and travels, what one eats and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various selenium concentrations. The 70-kg human is used for estimating intake.

1. Drinking Water

There are very limited data available for characterizing human intake of selenium from drinking water provided by public water supplies. Based on the information presented in Letkiewicz et al. (1984), it appears that, by far, most of the approximately 214 million people in the United States using public water supplies are exposed to levels below 5 μg/L. While some may be exposed to drinking water with no selenium present, information available from one survey suggests that most supplies do have selenium present at levels above 1 μg/L. There are too few data to reliably estimate the number of persons exposed to selenium in drinking water at various levels below 10 μg/L, the current MCL. Based on the compliance monitoring data available through Federal Reporting Data System (FRDS), it can be estimated that approximately 250,000 people are receiving drinking water from public water supplies with selenium levels above 10 μg/L, of which approximately 84% consume water from groundwater supplies.

2. Diet

Several estimates have been made of daily dietary intake of selenium in the United States. These are presented in Table IV-1. The estimates

Table IV-1. Reported Daily Dietary Intake of Selenium.

Source	Age	Area of country	Year	Daily intake (µg/day)
FDA 1980a, FDA 1982a	Adult	All	1978-79	157.3
			1977-78	156.2
			1976-77	110.7
			1975-76	135.6[a]
			1974-75	169.7[a]
			1973-74	169.0[a]
FDA 1980b, FDA 1982b	Infant (6 months)	Northeast	1976-77	11.3
		South	1976-77	10.9
		North Central	1976-77	15.1
		Western	1976-77	23.0
		All	1978-79	15
			1977-78	18
			1976-77	15.1
			1975-76	10.8[a]
			1974-75	21.6[a]
	Toddler (2 years)	Northeast	1976-77	54.0
		South	1976-77	37.9
		North Central	1976-77	43.1
		Western	1976-77	50.1
		All	1978-79	45
			1977-78	52
			1976-77	46.3
			1975-76	45.0[a]
			1974-75	58.4[a]
ICRP 1975	--	Seleniferous	--	0.01-0.1 mg/kg[a]
	--	--	--	150 (range 50-350)[a]
	Breast fed infant (6 months)	Nonseleniferous	--	17
Konz 1979	--	--	--	60-200[a]
Zabel et al. 1978	Infant (commercial formula diet)	--	--	5-35
Heit 1977	--	Seleniferous	--	600-6,340[a]

---

[a] May include drinking water.

generally place daily selenium intake in the range of 100 to 200 μg for adults, 40 to 60 μg for toddlers and 10 to 25 μg for infants.

In the most recent FDA market basket survey (FDA 1982a), it was found that 88% of the selenium intake by adults was estimated to be from the meat, fish and poultry group and the grain and cereal group. Dairy products were also a significant selenium source (10%).

3. Air

Konz (1979) indicated the intake of selenium from air to be 0.02 μg/day, 0.07 μg/day and less than 1 μg/day, based on information from three sources. Relative to the intake of selenium from food and drinking water, the intake from air appears to be insignificant.

B. Summary

There is a limited data base on human exposure to selenium from drinking water, food and air. While some information is available to suggest the general range of selenium intake from these three media, it is not possible to determine what proportion of the population have drinking water, dietary and respiratory intakes at various levels. For drinking water, it is possible to estimate the size of the population exposed to levels in public water supplies above 10 μg/L, the current MCL, but not for various levels at or below

10 µg/L. Consequently, a detailed relative source contribution assessment that describes the importance of each medium as a selenium source for different segments of the U.S. population could not be developed.

While it is not possible to develop a detailed profile of human exposure and the relative source contributions from the three media of interest of selenium, it is possible to describe the relative importance of the three media for typical exposure conditions.

The available information strongly indicates that food is the predominant source of selenium for most individuals. Using the most recent FDA market basket data, the dietary intake of selenium for the adult male is estimated to be approximately 105 µg/day. Assuming 90% absorption (Konz 1979) and a body weight of 70 kg, the dose from food is 1.9 µg/kg/day. Compared to the dose from food, the dose from air is relatively insignificant: assuming a daily intake of 0.07 µg (see Section IV.A.3) and an absorption rate of 70% (Konz 1979), the respiratory dose is only 0.0007 µg/kg/day, which is less than 0.05% of the dose from food. For a drinking water level of 5 µg/L, assuming a consumption of 2 L/day and 90% absorption, the dose would be 0.13 µg/kg/day, which is 6.7% of the food dose. Even at the current MCL of 10 µg/L, drinking water would contribute only 10% to 15% of the typical daily dose for the adult male.

V. HEALTH EFFECTS IN ANIMALS

A. Animal Nutritional Requirements

Congenital "white muscle" disease and nutritional myopathy in lambs and calves have been associated with selenium-deficient diets. Muth et al. (1958) noted the prevention of prenatal myopathy in lambs when 0.1 mg/kg of selenium (Na_2SeO_3) was added to diets of dystrophogenic pregnant ewes. Muscular dystrophy in lambs from dystrophogenic ewes was prevented by the addition of selenium (0.1 to 1 mg/kg per day) to the feed of ewes during late gestation (Muth et al. 1958). The addition of 0.5 mg/day of selenium to the diet (Hogue et al. 1962) also prevented dystrophy in lambs from mothers on a dystrophogenic diet. Selenium dietary requirement in livestock have been summarized in Table V-1. Insufficient selenium intake has also been implicated in the etiology of a group of selenium-responsive diseases in livestock which include muscular weakness of the newborn, immunosuppression, unthriftiness, reduced weight gain, scours, infertility, abortion and retained placenta (Van Vleet 1980).

In laboratory animals, observations by Schwarz (1951b) suggested that a factor (called Factor 3) present in American baker's yeast was essential in preventing necrosis and degeneration of the liver in rats given a diet free of vitamin E and low in sulfur amino acids. The essential component of Factor 3 was found to be selenium.

Schwarz (1951a) showed that although baker's yeast was an excellent source of Factor 3, torula yeast was completely devoid of this antinecrogenic factor.

Table V-1. Selenium Dietary Requirements in Livestock.[a]

Animal	Dietary Requirements (mg Se/kg of feed)
Cattle	0.10
Sheep	0.10
Swine	0.10
Poultry	0.15
Turkey	0.20

[a] Adapted from Patrias (1969) and Fishbein (1977).

In the mouse, necrosis and degeneration were not confined to the liver but were found in the heart, kidneys, skeletal muscle and pancreas. Death was the result of cardiac failure (Schwarz 1961).

Several methods are available for supplementing livestock with selenium. These include selenium-containing injectables and drenches or treatment of feeds and salt mixes with selenium. Selenium deficiency in animals has been prevented by dietary selenium levels of 0.02 to 0.2 μg/g of dry diet (Levander 1976). The species being tested and other factors enter into the ultimate determination of the optimal selenium concentration. A highly successful and practical method of preventing and/or treating selenium deficiency in cattle is by the addition of selenium to a salt mixture (Koller et al. 1983).

Diplock (1976a) has reviewed a number of studies concerned with the nutritional roles of selenium in laboratory and domestic animals. A deficiency of selenium (Factor 3 of baker's yeast) has been shown to produce hepatic necrosis in rats, exudative diathesis in poultry, hepatosis dietetica in swine, and skeletal muscle degeneration in poultry, domestic animals and laboratory rodents.

Witting and Horwitt (1964) note that normal growth in rats requires a narrow optimal range of selenium concentration. The best growth rate in this study, using tocopherol-deficient rats, was found with the addition of 0.1 mg/kg of selenium in the form of selenite. A concentration of 0.3 mg/kg of selenium produced a better growth rate than 0.03 mg/kg, but not as good as 0.1 mg/kg.

Thompson and Scott (1970) have established selenium as an essential micronutrient for the chicken. The ability of selenium to prevent pancreatic degeneration (which occurs in selenium-deficient chickens) appears to be dependent on the dietary level of vitamin E. In general, the dietary requirements for selenium of mammalian species appear to be at a level of 0.1 mg Se/kg of food (NAS 1971, NAS 1980b, Levander 1976).

B. Acute Toxicity

1. Livestock

"Blind staggers" is the disease resulting from acute toxicity of selenium in cattle and other livestock after eating seleniferous plants. The animal exhibits impaired vision, difficulty in judging the closeness of objects and a tendency to wander aimlessly. Paralysis and abdominal pain occur in the final stages. Death is usually the result of respiratory failure (Browning 1969). Table V-2 summarizes the dose studies related to acute toxicity of selenium in livestock.

Dudley (1936) reported that 19.6 mg/kg body weight (bw) of selenium (in the form of sodium selenite) administered as a single oral dose was fatal to pigs in three days. In the same report, a single oral dose of 20.0 mg of selenium/kg-bw (as sodium selenite) proved fatal to a calf in six hours. Miller and Williams (1940) noted a minimum lethal dose of selenium (single dose) to be 1.5 mg/lb bw (3.3 mg/kg-bw) for horses; 4.5 to 5 mg/lb bw (9.9 to 11 mg/kg-bw) for cattle; and 6 to 8 mg/lb bw (13.2 to 17.6 mg/kg-bw) for swine.

Table V-2. Acute Selenium Toxicity in Livestock.

Compound	Animal[a]	Route[b]	Duration of Study	Toxicity	Reference
Sodium selenite	Swine (1)	Oral	3 days	19.6 mg Se/kg-bw Death in 3 days	Dudley (1936)
Sodium selenite	Calf (1)	Oral	6 hours	20.0 mg Se/kg-bw Death in 6 hours	Dudley (1936)
Sodium selenite	Horse, mule (7)	Oral	4 days	3.3 mg Se/kg-bw Min. lethal dose	Miller and Williams (1940)
Sodium selenite	Cattle (4)	Oral	4 days	9.9 mg Se/kg-bw Min. lethal dose	Miller and Williams (1940)
Sodium selenite	Swine (7)	Oral	4 days	15.0 mg Se/kg-bw Min. lethal dose	Miller and Williams (1940)
Sodium selenite	Swine (NS)[c]	s.c. injection	4 hours	2.0 mg Se/kg-bw Death in 4 hours	Orstadius (1960)
Sodium selenite	Swine (NS)	s.c. injection	5 days	1.2 mg Se/kg-bw Death in 5 days	Orstadius (1960)
Selenium containing plant material	Sheep (1)	Oral	20 hours	11.2 mg Se/kg-bw Death in 20 hours	Dudley (1936)

[a] Number of animals in parenthesis.
[b] Single dose administered.
[c] NS = Not specified.

A single subcutaneous dose of selenite (2 mg Se/kg-bw) in swine produced 100% mortality in four hours (Orstadius 1960). The lowering of the Se dose to 1.2 mg Se/kg-bw produced 100% mortality in 5 days.

2. Laboratory Animals

Acute selenium poisoning in laboratory animals has been produced by doses of a selenium compound administered orally, subcutaneously (s.c.), intraperitoneally (i.p.), or intravenously (i.v.). Sodium selenite and selenate are the most commonly tested selenium salts. Different observers have reported different lethal doses. This is probably due to species differences, age of animals, mode of administration, and the purity of the salts (Fishbein 1977). Fishbein (1977) provides an extensive review of the early literature on the acute effects of selenium. Since acute effects are not used as the basis for risk assessment, the following discussion draws heavily upon Fishbein's review.

Tables V-3 and V-4 summarize the acute toxicity of selenium compounds in rats and rabbits, respectively. The minimum lethal dose of sodium selenite (in mg Se/kg-bw) has been reported by Moxon and Rhian (1943) as 3.0 to 5.7 for the rat, 0.9 to 1.5 for the rabbit and 2.0 for the dog. These values represent subcutaneous, intravenous, and intraperitoneal methods of administration, respectively. Using intraperitoneal injection, Franke and Moxon (1936) noted a minimum lethal dose of 3.25 mg Se/kg-bw with selenite and 5.25 mg Se/kg-bw with selenate. The minimum lethal dose in this early study was defined as the smallest dose of selenium compound that would kill 75% of the rat population studied within two days after exposure.

Table V-3. Acute Toxicity of Selenium in Rats.

Compound	Number of animals	Route	Length of exposure	Toxicity	Reference
Sodium selenite	155	i.p. injection	48 hours	MLD[a] 3.25 to 3.50 mg Se/kg/bw	Franke and Moxon (1936)[b]
Sodium selenite	45	i.v. injection	48 hours	MLD[c] 3.0 mg Se/kg-bw	Smith et al. (1937)[b]
Sodium selenate	NS[d]	i.p., i.v. and s.c. injections	NS[d]	MLD[c] 3.0 to 5.7 mg Se/kg-bw	Moxon and Rhian (1943)[b]
Sodium selenate	90	i.p. injection	48 hours	MLD[a] 5.25 to 5.75 mg Se/kg-bw	Franke and Moxon (1936)[b]
Sodium selenate	37	i.v. injection	48 hours	MLD[c] 3.0 mg Se/kg-bw	Smith et al. (1937)[b]
Diselenodipropionic acid (selenium-methionine)	16	i.p. injection	48 hours	LD_{50} 4.25 mg Se/kg-bw	Klug et al. (1949)
Trimethyl selenonium chloride	14	i.p. injection	4 hours	LD_{50} 49.4 mg Se/kg-bw	Obermeyer et al. (1971)

[a] Minimum doses fatal to at least 75% of test rats in 2 days
[b] Adapted from Fishbein (1977)
[c] Minimum lethal dose, not defined
[d] NS = Not specified

Table V-4. Acute Toxicity of Selenium in Rabbits.

Compound	No. of animals	Route	Length of exposure	Toxicity	Reference
Sodium selenite	9	i.v. injection	7 days	MLD[a] 1.5 mg Se/kg-bw	Smith et. al. (1937)[b]
Sodium selenate	16	i.v. injection	2 days	MLD[a] 2.0 to 2.5 mg Se/kg-bw	Smith et. al. (1937)[b]
Sodium selenite	NS[c]	i.p., i.v. and s.c. injection	NS[c]	MLD[a] 0.9 to 1.5 mg Se/kg-bw	Moxon and Rhian (1943)[b]
Selenium oxychloride	10	application to skin	various	Toxic dose is less than 7 mg $SeOCl_2$/kg-bw	Dudley (1938)

[a] Minimum lethal dose, not defined
[b] Adapted from Fishbein (1977)
[c] NS = Not Specified
[d] Observation period varied from 5 to 24 hours until death

Acute toxic hepatitis in rats has been pathologically characterized by liver surfaces that are mottled with pale yellow or white areas and with margins of the lobes that are strippled with pale foci (Harr et al. 1967). Parenchymatous degeneration was present. The cytoplasm of the hepatic cells was finely granular and eosinophilic.

The overall conclusion from the available literature is that there are minor variations from species to species in susceptability to acute selenium induced toxicity, and that selenite and selenate produce similar acute toxic effects.

C. Chronic Toxicity

1. Livestock

Chronic selenium poisoning in livestock usually results in a disorder referred to as "alkali disease." This disease is characterized by hair loss and deformation and sloughing of the hooves in livestock that have consumed moderate amounts of selenium over a prolonged period of time. Lambs are born with abnormal eyes, deformed feet, and myopathies. Lesions of internal organs are more marked in the heart (atrophy and decompensation) and liver (cirrhosis). The kidneys may show glomerulonephritis and erosion may occur in the joints of the long bones. There is also a high incidence of anemia (Browning 1969). Occasionally, affected animals may show some of the symptoms of "blind staggers" also associated with acute selenium poisoning.

Thapar et al. (1969) found that sodium selenite or selenious acid (8 mg Se/kg of feed) added to either a practical corn-soy diet or a Cerelose-soybean protein diet fed to laying hens reduced: (1) production, weight and hatchability of eggs, (2) body weight, (3) survival rate and (4) growth of progeny. The diet was fed from one day of age for as long as 105 weeks. No detrimental effects were observed when sodium selenite or selenious acid was added at the rate of 2 mg Se/kg of feed. Similar findings from experiments using sodium selenite were reported by Arnold et al. (1973).

The chronic toxic effects of selenium on livestock are summarized in Table V-5.

2. Laboratory Animals

The chronic toxicity of selenium in laboratory animals is summarized in Table V-6. Schroeder and Mitchener (1971a) have evaluated the toxic effects of selenate and selenite in rats. Selenium (2 mg/L) was added to the drinking water from the time of weaning until natural death. After a year the concentration was raised to 3 mg/L. Selenite was highly toxic, suppressed growth and caused high early mortality. Selenate was not as toxic in terms of growth and survival. Male rats were more susceptible to the effects of selenite than females.

Harr et al. (1967) fed sodium selenate and selenite daily to rats (Harr and Muth 1972). At concentrations up to 16 mg Se/kg of feed (initial dose of 1.6 mg Se/kg-bw/day; assuming bw = 0.10 kg and feed/day = 0.01 kg), rats grew slowly and died within 90 days while those on rations containing 0.5 mg Se/kg

Table V-5. Chronic Toxicity of Selenium in Livestock.

Compound (Animal)	Route	Dose	Duration of study	Effects	Reference
Sodium selenite (cattle)[a]	oral	0.55 to 1.1 mg Se/kg-bw (3 doses/week)	28 weeks	2 animals died in 8 weeks, 4 died in 20 to 23 weeks, 2 survived, until termination of the experiment at 28 weeks	Maag et al. (1960)
Sodium selenite (chickens)[b]	oral	8 mg/kg of feed	105 weeks	Reduced egg production, weight, hatchability of eggs	Thapar et al. (1969)
Sodium selenite (chickens)[b]	oral	2 mg/kg of feed	105 weeks	No detrimental effects in chickens or eggs	Thapar et al. (1969)

[a] Eight animals were administered selenium in feed.

[b] Two groups of 25 chickens per dose level.

Table V-6 Chronic Toxicity of Selenium in Laboratory Animals.

Compound	Animal	Route and dose	Length of exposure	Effects	Reference
Sodium selenite	Rats (male, young post-weanling)	1.6 to 11.2 mg Se/kg of feed	6 weeks	Growth not affected below 3.2 mg Se/kg. At 6.4 mg Se/kg and above, pathologic changes were noted	Halverson et al. (1966)
Sodium selenite	Rats	0.75 mg/kg of feed	2 years	Minimal toxic dose based on longevity	Harr and Muth (1972)[a]
Sodium selenite	Rats	6 to 16 mg/kg of feed	90 days	Died before 90 days of exposure	Harr and Muth (1972)[a]
Sodium selenite	Rats	4 mg/kg of feed	2 years	Grew slowly, 10% survived 15-24 months	Harr and Muth (1972)[a]
Sodium selenite	Rats	0.5 mg/kg of feed	2 years	Grew well, lived as long as controls (contained hyperplastic liver lesions)	Harr and Muth (1972)[a]
Sodium selenite or selenate	Rats (male)	2 mg/L in drinking water	6 weeks	No effect	Palmer and Olson (1974)
Sodium selenite	Rats (male)	6 mg/L in drinking water	6 weeks	Four of six rats died by six weeks	Palmer and Olson (1974)

continued-

---

[a] Summarized results of Harr et al, (1967).

Table V-6 - continued

Compound	Animal	Route and dose	Length of exposure	Effects	Reference
Sodium selenite	Rats (male)	9 mg/L in drinking water	6 weeks	Six of six rats died by six weeks	Palmer and Olson (1974)
Sodium selenate or selenite	Rats (male)	3 mg/L in drinking water	6 weeks	No effect	Palmer and Olson (1974)
Sodium selenate	Rats (male)	6 mg/L in drinking water	6 weeks	One of six rats died by six weeks	Palmer and Olson (1974)
Sodium selenate	Rats (male)	9 mg/L in drinking water	6 weeks	Five of six rats died by six weeks	Palmer and Olson (1974)
Ammonium potassium selenide	Rats (female)	5 µg/g in corn or wheat	2 years	17 of 36 rats died	Nelson et al. (1943)
		7 µg/g in corn or wheat	2 years	26 of 36 rats died	
		10 µg/g in corn or wheat or as selenide	2 years	44 of 54 rats died	

of feed (initial dose of 0.05 mg Se/kg-bw/day) survived two years. Livers from the latter animals contained hyperplastic lesions. However, rats fed 0.5 mg Se/kg of feed grew as well as the controls. A dose of 2.0 mg Se/kg of feed (initial dose of 0.2 mg Se/kg-bw/day) resulted in hepatic cirrhosis. It was noted that pathologic changes occurred in the liver of rats fed 0.25 mg Se/kg of feed (initial dose of 0.03 mg Se/kg-bw/day). The minimum toxic level based on longevity and lesions in the heart, kidneys and spleen was concluded to be 0.75 mg/kg (initial dose of 0.08 mg Se/kg-bw/day).

Post-weaning rats fed sodium selenite or naturally occurring selenium-containing grain diets (1.6 to 11.2 mg/kg of feed) for six weeks were studied for pathologic changes (Halverson et al. 1966). At selenium concentrations below 3.2 mg/kg of feed (0.28 mg Se/kg-bw/day; based upon reported animal weight and food consumption data and assuming average bw = 0.15 kg and feed/day = 0.013 kg) for sodium selenite and below 6.4 mg/kg of feed (0.55 mg Se/kg-bw/day) for selenium-containing grain, growth was not affected. At selenium concentrations at or above 8.0 mg/kg of food (0.68 mg Se/kg-bw/day; assuming average bw = 0.13 and feed/day = 0.011 kg), restriction of food uptake, increased mortality, enlargement of the spleen, enlargement of the pancreas, reduced liver-to-body weight ratios and decreased blood hemoglobin were noted.

Palmer and Olson (1974) administered sodium selenite (2 mg/L) or sodium selenate (3 mg/L) in the drinking water of rats for 6 weeks. Neither concentration produced mortality, although a slight decrease in growth was noted.

When rats were given concentrations of 6 mg/L and 9 mg/L (both as sodium selenite and sodium selenate in the drinking water), 5 of 12 rats died at the lower dose, and 11 of 12 rats died at the higher dose after six weeks. Although more rats receiving selenite died than those receiving selenate, the authors concluded that the toxicity of the two forms was similar overall.

Nelson et al. (1943) designed a study to determine the lowest dietary concentration of selenium necessary to produce chronic toxicity. Seven groups of 18 female rats each (inbred Osborne-Mendel strain) were fed selenium either in organic combination with corn and wheat or in a mixed inorganic selenide solution (a solution of ammonium potassium sulfide and ammonium potassium selenide, containing 48 g of selenium per liter of solution). Beginning at three weeks of age, the rats received selenium at levels of 5, 7 and 10 µg/g of diet. Mortality was high at all doses and found to be approximately proportional to the level of dietary selenium (Table V-6). Only 53 of the 126 selenium-fed rats of all doses survived for 18 months; 39 survived for 24 months.

D. Synergism/Antagonism

A comprehensive survey of the synergistic and antagonistic properties of selenium in combination with other compounds is beyond the scope of this document. This is because there is no consensus on how such combination effects should be incorporated into the risk assessment process. However, to ensure the reader is aware of the significant synergistic and antagonistic properties unique to selenium, the following survey of selected literature references on this topic is provided.

Selenium has been demonstrated to be antagonistic to a variety of toxic compounds when added either preceding or concurrently with the toxic compound. The toxic effects of metals such as silver (Grasso et al. 1969), arsenic (Levander and Baumann 1966), cadmium (Kar et al. 1960), and mercury (Levander and Argrett 1969) have been offset by the simultaneous exposure to the heavy metals and selenium. Sulfate (Halverson et al. 1962) and vitamin E combined with methionine (Levander and Morris 1970), when added to the diet, protected rats from the toxic effects of selenium.

Moxon and Dubois (1939) demonstrated that fluoride increases the toxicity of selenium in rats. They added 5 mg/L of fluoride to the drinking water of rats fed a diet containing selenium at 11 μg/g as seleniferous grain. Mortality increased while weight gains and food and water intake decreased. These findings were not reproducible, however (Hadjimarkos 1965).

Diplock et al. (1967) and Grasso et al. (1969) found that 0.15% silver acetate in the drinking water produced toxic symptoms in weanling rats and chickens fed vitamin E-deficient diets. The rats suffered from dystrophic lesions, necrosis of the liver and high mortality. Chickens suffered a pro-exudative effect. Supplementation with 0.05 mg Se/kg had little effect, whereas the addition of 1 mg Se/kg to the diet resulted in 55% protection against the toxic effects of silver. Grasso et al. (1969) observed that the lesions produced in the liver by silver and the lesions caused by dietary deprivation of vitamin E and selenium were similar.

Rusiecki and Brzezinski (1966) found that oral administration of selenate prevented the toxicity of thallium and that the content of thallium in liver, kidneys, and bones was increased by the selenate. Levander and Argrett (1969) showed that subcutaneous injection of thallium acetate increased the retention of selenium in liver and kidney and decreased the pulmonary and urinary excretion of selenium.

Rats fed a basal Se-deficient diet or a diet supplemented with 0.5 or 2.0 mg Se/kg of feed for 40 days were injected (i.p.) with 25 mg paraquat dichloride/kg-bw (Omaye et al. 1978). Fifty percent of the rats on the Se-deficient diet died four hours after paraquat treatment, while all rats fed a Se-supplemented diet survived.

Halverson and Monty (1960) have demonstrated that dietary sulfate will partially restore the growth of selenium-poisoned rats receiving a purified diet with selenium added as selenite or selenate. Sulfate levels of 0.29%, 0.58%, and 0.87% as sodium or as potassium salts progressively relieved the growth inhibition due to selenium. Alleviations of greater than 40% were observed. Sulfate, however, did not substantially prevent liver degeneration due to selenium. In a later study, Halverson et al. (1962) found that protection of liver necrosis was provided by the addition of sodium sulfate to diets containing 10 mg Se/kg when present as selenate, but not when present as selenite or as wheat containing selenium. A similar but less pronounced protective effect was observed with sodium thiosulfate and sodium sulfite added to the seleniferous diets.

Levander and Morris (1970) used a peanut-meal diet and found that neither methionine nor vitamin E alone gave much protection against hepatic damage produced by excessive selenium. Combinations of methionine and vitamin E were effective, and the degree of protection was approximately proportional to the concentration of vitamin E added to the diet. The concentrations of selenium in the liver and kidneys of rats fed the diets supplemented with methionine and vitamin E were less than those of rats fed either methionine or vitamin E alone and of rats that received no supplement.

Moxon (1938) established that the chronic and acute toxicity produced in rats by feeding grains containing selenium at 15 mg Se/kg could be alleviated or prevented by administration of sodium arsenite at 5 mg/L in the drinking water. It was shown that arsenate or arsenite were equally effective, and the selenium could be present as seleniferous grain, selenite, or selenocystine (Moxon et al. 1944, 1945, 1947, Dubois et al. 1940, Thapar et al. 1969, Ganther and Baumann 1962). Ganther and Baumann (1962) administered subacute dosages of arsenite and selenite and found that excretion of selenium into the gastrointestinal tract was stimulated by arsenite. Levander and Baumann (1966) demonstrated that selenium is excreted in the bile of arsenic-treated animals. When $NaAsO_2$ was administered at doses varying from 0 to 2 mg As/kg-bw, it resulted in a progressive decrease in the liver concentration of selenium in treated rats (0.5 mg Se/kg as $Na_2{}^{75}SeO_3$). In the same study, arsenic produced a tenfold increase in the biliary excretion of selenium in rats with acute biliary fistulas. When the arsenic-to-selenium dose ratio was maintained at two, arsenic was shown to have an effect on biliary excretion of selenium when the dietary level of selenium was as low as

0.02 mg Se/kg. Levander (1972) suggested that arsenic protection against selenium toxicity may be mediated by the combination of arsenic with selenium in the liver to form a conjugate that is readily excreted into the bile.

Kar et al. (1960) found that parenterally administered cadmium-induced lesions in the testes of rats could be prevented by the administration of selenium. Mason and Young (1967) reported that protection against the testicular injury produced by single subcutaneous injections of 0.45 mg of cadmium chloride in rats was provided by the concurrent injection of half-equimolar selenium dioxide. Minimal protection was provided by daily subcutaneous injections of half-equimolar selenium dioxide given over six successive days before cadmium administration. Parizek et al. (1968) found that the mortality rates of rats given otherwise lethal doses of cadmium, parenterally, were much reduced by the administration of selenium. Kar et al. (1960) and Parizek et al. (1968) found that selenium would prevent parenterally administered cadmium damage to the nonovulating ovary in the rat. Parizek et al. (1968) reported that administration of selenium could prevent necrosis and destruction of the placenta caused by exposure to small amounts of parenterally administered cadmium near the end of pregnancy.

Levander and Argrett (1969) described the effect of various mercury salts on the metabolism of selenium. Parizek and Ostadalova (1967) demonstrated that small amounts (0.03 mmole/kg-bw) of sodium selenite (Na_2SeO_3), when given to rats intoxicated by a lethal dose (0.02 mmole/kg-bw) of mercury ($HgCl_2$), completely protected the kidneys or intestines of these animals and ensured their survival. Levander and Argrett (1969) reported that mercury increased the retention of selenium in the blood, kidneys, and spleen. Parizek et al. (1971b) found that the transport of mercury across the placenta in pregnant rats was decreased by selenium, and that less mercury was secreted into the milk. The bioavailability of selenium was much lower in the rats treated with mercury. Ganther et al. (1972) showed that Japanese quail given 20 mg Hg/kg as methylmercury in diets containing 17% tuna (by weight) survived considerably longer than quail given the same amount of methylmercury in a corn-soya diet. It was also found that when a number of different batches of tuna were analyzed for mercury and selenium, there was a striking correlation between the levels of selenium and mercury. Those batches that had little selenium contained little mercury (1.91 mg Se/kg: 0.32 mg Hg/kg), and when the mercury level was high, the selenium level was also high (2.91 mg Se/kg: 2.87 mg Hg/kg). These results suggest that the higher selenium content of the tuna-supplemented diet acted to reduce the toxic effect of the additional methylmercury ingested by the quail.

E. Teratogenicity

There is evidence that selenium, in at least some of its chemical forms, is teratogenic and embryotoxic in certain animal species, particularly the chicken. This has been established in early controlled laboratory experiments on chicken embryos by Franke et al. (1936). Information presented here on nonmammalian teratology is intended to demonstrate the potential biological behavior of selenium, which may correlate with less-well-documented teratology data in mammals, in which selenium has been incriminated. A summary of the key teratology data for selenium is presented in Table V-7.

Table V-7 Teratology in Animals Chronically Exposed to Selenium.

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Effect of treatment	Reference
Sodium selenite	2 mg/L	30 days prior to gestation to day 18 of gestation	Drinking water	IVCS mice	No effect	Nobunaga et al. (1979)
Sodium selenite	4 mg/L	30 days prior to gestation to day 18 of gestation	Drinking water	IVCS mice	Few gross malformations, cleft palate and/or micrognathia. Retardation of fetal growth	Nobunaga et al. (1979)
Sodium selenite	2 mg/kg	Days 7-12 of gestation	s.c.	ICR mice	No effect	Lee et al. (1979)
Sodium selenite	2 mg/kg	Days 9-12 of gestation	s.c.	ICR mice	No effect	Lee et al. (1979)
Sodium selenite	3.5 mg/kg	Days 7-12 of gestation	s.c.	ICR mice	Reduced fetal weight	Lee et al. (1979)
Sodium selenite	3.5 mg/kg	Days 9-12 of gestation	s.c.	ICR mice	No effect (fetal weight not reported)	Lee et al. (1979)
Sodium selenite	3.5 mg/kg	Day 10 of gestation	s.c.	ICR mice	No effect	Lee et al. (1979)
Selenate	3 mg/L	Continuous in water for 3 generations	Drinking water	CD mice	Decrease in number of litters in the F_3 generation, runts born in the F_3, stillborn litter. The male-female ratio increased over controls	Schroeder and Mitchener (1971b)

continued-

Table V-7- continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Effect of treatment	Reference
Sodium selenite	2 mg/kg	One injection on day 8 of gestation	i.v.	Golden hamster	No effect	Holmberg and Ferm (1969)
Selenium of undetermined form	Variable dose related to effect	Prior to mating	Selenized diets	Rats	Affected growth and reproduction	Munsell et al. (1936)
Potassium selenate	1.5 mg/L	Prior to/during/after gestation for 2 generations	Drinking water	Rats	No effect	Rosenfeld and Beath (1954)
Potassium selenate	2.5 mg/L	Prior to/during/after gestation for 2 generations	Drinking water	Rats	Number of young by mothers decreased 50% in second generation	Rosenfeld and Beath (1954)
Potassium selenate	7.5 mg/L	5 to 8 days prior to parturition	Drinking water	Rats	Decrease in surviving offspring continued on selenium treatment	Rosenfeld and Beath (1954)
Potassium selenate	7.5 mg/L	Prior to mating	Drinking water	Rats	Females failed to conceive	Rosenfeld and Beath (1954)
Sodium selenite	22.3 mg/kg of feed 33.5 mg/kg of feed	Prior to mating	Selenized wheat diets	Wistar rats	Infertile, female unable to rear young. The only fertile matings occurred when only one partner was on selenized diet	Franke and Potter (1935, 1936)

continued-

Table V-7 - continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Effect of treatment	Reference
Selenious acid	0.03 mg/egg[a]	One injection on day 4 of incubation	Yolk sac	White Leghorn chicken	Abnormalities in 10-20% of embryos surviving to 18 days of incubation	Ridgway and Karnofsky (1952)
Selenious acid	0.10 mg/egg[a]	One injection on day 8 of incubation	Yolk sac	White Leghorn chicken		Ridgway and Karnofsky (1952)
Selenious acid	0.02 mg/egg[a]	Day 8 of incubation	Chorio-allantic membrane	White Leghorn chicken		Ridgway and Karnofsky (1952)
Potassium selenite	0.47 mg/kg/egg[a]	One injection to 14-day embryos	Air cell of eggs	White Leghorn chicken	Swelling of dorsal portion of the neck of a few surviving embryos	Halverson et al. (1965)
Sodium selenite	0.51 mg/kg/egg[a]	One injection to 14-day embryos	Air cell of eggs	White Leghorn chicken		Halverson et al. (1965)
Potassium selenate	2.00 mg/kg/egg[a]	One injection to 14-day embryos	Air cell of eggs	White Leghorn chicken		Halverson et al. (1965)
Sodium selenate	1.76 mg/kg/egg[a]	One injection to 14-day embryos	Air cell of eggs	White Leghorn chicken		Halverson et al. (1965)

continued-

---

[a] Dose is the LD_{50}

Table V-7 - continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Effect of treatment	Reference
Sodium selenite	0.3 mg/kg/egg[a]	One injection on day 4 of incubation	Air cell of eggs	Chicken	Sodium selenite and sodium selenate produced most of the abnormalities, the other compounds-produced only a few. Underdeveloped beak and abnormal development of feet and legs. Fusing or webbing of two outside toes most common. Extreme abnormalities such as fusing of foot into one large toe resulted	Palmer et al. (1973)
Trimethylselenonium chloride	15.7 mg/kg/egg[a]	One injection on day 4 of incubation	Air cell of eggs	Chicken		Palmer et al. (1973)
Trimethylsulfonium iodide	4.4 mg/kg/egg[a]	One injection on day 4 of incubation	Air cell of eggs	Chicken		Palmer et al. (1973)
Sodium selenate	0.13 mg/kg/egg[a]	One injection on day 4 of incubation	Air cell of eggs	Chicken		Palmer et al. (1973)
Selenomethionine	0.13 mg/kg/egg[a]	One injection on day 4 of incubation	Air cell of eggs	Chicken		Palmer et al. (1973)
Selenocystine	0.64 mg/kg/egg[a]	One injection on day 4 of incubation	Air cell of eggs	Chicken		Palmer et al. (1973)
Se-methylcysteine	0.57 mg/kg/egg[a]	One injection on day 4 of incubation	Air cell of eggs	Chicken		Palmer et al. (1973)

continued-

---

[a] Dose is the LD_{50}

Table V-7 - continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Effect of treatment	Reference
Methyl seleninic acid	0.052 mg/kg/egg[a]	One injection on day 4 of incubation	Air Cell of eggs	Chicken		Palmer et al. (1973)
Dimethyl selenoxide	6.53 mg/kg/egg[a]	One injection on day 4 of incubation	Air Cell of eggs	Chicken		Palmer et al. (1973)
Sodium selenate	0.6 mg/kg	One injection prior to incubation	Air cell of fertile egg	Chicken	Shortened upper beak, feet undeveloped eyes and upper beak missing, encephalocoels, ectopias	Franke et al. (1936)
Sodium selenate	0.6 to 0.8 mg/kg	One injection prior to incubation	Air cell of fertile egg	Chicken	Worse effects than 0.6 mg/kg with sodium selenate	Franke et al. (1936)
Sodium selenite	0.01 mg/kg	One injection prior to incubation	Air cell of fertile egg	Chicken	Mild effects similar to 0.6 mg/kg with sodium selenate	Franke et al. (1936)
Sodium selenate	0.1 mg/kg	One injection prior to incubation	Air cell of fertile egg	Chicken	Same as 0.6 mg/kg sodium selenite	Franke et al. (1936)
Sodium selenite	0.6 to 0.8 mg/kg	One injection prior to incubation	Air cell of fertile egg	Chicken	Worse effects than 0.6 mg/kg with sodium selenate	Franke et al. (1936)

continued-

Table V-7 - continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Effect of treatment	Reference
Sodium selenite	0.8 mg/kg	One injection prior to incubation	Air cell of fertile egg	Chicken	Embryo development entirely prevented or high mortality	Franke et al. (1936)
Selenium of undetermined form	6 to 18 mg/kg of embryo tissue	Exposure of adults prior to hatching	Diet of adult	Chicken	Similar to observations presented above in Franke et al. (1936)	Poley et al. (1937)
Selenium of undetermined form	0.5 to 1.0 mg/day	Exposure of adults prior to hatching	Diet of adult	Creeper mutant hens bred to Leghorn cocks	Amplification of the mutations typical of creeper fowl and increased embryonic mortality	Landauer (1950)
Selenium of undetermined form	2.5 mg/kg of feed	Exposure of adults prior to hatching	Diet of adult (toxic grain)	Chicken	Normal hatchability	Poley and Moxon (1938)
Selenium of undetermined form	5 mg/kg of feed	Exposure of adults prior to hatching	Diet of adult (toxic grain)	Chicken	Slightly reduced hatchability	Poley and Moxon (1938)
Selenium of undetermined form	10 mg/kg of feed	Exposure of adults prior to hatching	Diet of adult (toxic grain)	Chicken	Zero hatchability, a few hatched and died, a few more were normal	Poley and Moxon (1938)

continued-

Table V-7 - continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Effect of treatment	Reference
Selenium of undetermined form	8 mg/kg of feed	Exposure of adults prior to hatching	Diet of adult	Chicken	Necrosis, focal growth retardation, generalized growth retardation. Gross abnormalities similar to Franke et al. (1936)	Gruenwald (1958)
Sodium selenite	0.5 to 1 mg/L	1 to 14 days	In the water in which eggs were hatched	Frog (*Xenopus laevis*)	Below 1 mg/L no signs of toxicity were seen	Browne and Dumont (1979, 1980)
Sodium selenite	2,5,10, 20 mg/L	1 to 14 days	In the water in which eggs were hatched	Frog (*Xenopus laevis*)	Variable mortalities were seen depending on the stage of development and the days exposed. Early eggs were less resistant. Abnormalities including flattened, irregular heads,curved spines and tails, and epidermal blisters were seen. Somites and muscle cells were degenerating	Browne and Dumont (1979, 1980)

continued-

Table V-7 - continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Effect of treatment	Reference
Sodium selenite	10 mg/kg	Prior to/during/after conception	Diet	Swine	Lowered conception rate, decreased number of surviving offspring, lower birth weight, and significantly reduced weights of offspring at 56 days postpartum.	Wahlstrom and Olson (1959)
Selenium of undetermined form	Unknown	To adults prior to birth	Seleniferous range sources in diet	Sheep	Pathologic changes similar to blind staggers type of poisoning	Beath et al. (1939)
Selenium of undetermined form	Unknown	To adults prior to birth	Seleniferous range sources in diet	Sheep	75% of malformed animals died at birth and 10% died at 3 to 5 months	Rosenfeld and Beath (1947)
Selenium of undetermined form	Unknown	To mother prior to birth	Diet of adult	Horse	Congenital alkali disease in a 14-day old colt born to a mare with similar symptoms during gestation	Smith et al. (1936)

It is apparent from Table V-7 that for hens, selenite in the feed at levels of 8 to 10 mg/kg can result in an increased percentage of fetal deaths and extensive malformations of the central nervous system, extremities and beak. Exposures to seleniferous feeds resulting in fetal tissue levels of 6 to 18 mg/kg cause a similar level of abnormalities (Poley et al. 1937). Direct injection of selenite into eggs at levels as low as 0.01 mg/kg can result in similar types of abnormalities, but to a lesser degree than those produced by higher injected doses, such as 0.6 to 0.8 mg/kg (Franke et al. 1936). There seems to be some variability in the toxic response that is related to the time of toxic exposure (Ridgway and Karnofsky 1952, Halverson et al. 1965). That is, older chicken fetuses tend to be more resistant than younger fetuses. Selenate is also toxic to chick embryos, but whether selenate is slightly more toxic than selenite (Palmer et al. 1973) or the reverse (Halverson et al. 1965) is unclear. Organic selenium compounds such as trimethylselenonium chloride are much less toxic than selenite (Palmer et al. 1973).

It can also be seen in Table V-7 that selenite in ambient water poses teratogenic and embryocidal risks for developing aquatic organisms. Frog (Xenopus laevis) embryos are highly sensitive to sodium selenite ambient water concentrations above 1 mg/L with an LD_{50} between 1 and 2 mg/L (Browne and Dumont 1979, 1980).

There is considerably more difficulty in establishing a similar relationship for mammalian embryos and fetuses. Referring to Table V-7, it can be determined that early observations on livestock (i.e., sheep and horses) exposed to seleniferous feed and raised on a seleniferous range implicated selenium in a wide range of teratological effects. The most notable study of this type that can be verified is that of Rosenfeld and Beath (1947) in which anomolies of the eyes and joints of the extremities and hypoplasia of reproductive organs were noted. Unfortunately, the dose levels, the form of the selenium compound, and interfering substances such as mercury, arsenic, cadmium and sulfate were not determined. It is interesting to note that other published observations of this type report that the offspring of sheep and horses who grazed on a seleniferous range had congenital toxic syndromes similar to those in affected adults. These syndromes include "alkali disease" (Smith et al. 1936).

When investigators have conducted controlled studies to evaluate the teratological effects in mammals, the results were not as marked as those seen in chickens. Rats chronically exposed to sodium selenite in the water did not develop teratologic malformations. There was an indication, however, that reproduction was affected at selenite concentrations of 2.5 to 7.5 mg/L in the drinking water, and the survival of the young was affected after birth (Rosenfeld and Beath 1954). However, as shown in Table V-7, concentrations of 2 mg/L in the drinking water and 2 mg/kg-bw by injection seem to have no effect on developing mammalian fetuses. At doses of 4 mg/L in the the drinking water or 3.5 mg/kg-bw by injection, only mild retardation of fetal growth was produced (Nobunaga et al. 1979, Holmberg and Ferm 1969, Lee et al. 1979).

To evaluate the apparent discrepancy between chicken or frog embryo toxicity and mammalian resistance, Table V-8 summarizes information on the

Table V-8. Selenium Transfer from Mother to Egg or to Mammalian Fetus Across the Placenta.

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Distribution to Fetus, Embryo, Egg	Reference
Natural selenium	0.42 mg/kg of feed	Prior to and during egg laying	Diet	Chicken	Distribution to egg higher than that of sodium selenite supplemented diets	Latshaw (1975)
(Mixed) Natural selenium and selenite selenium	0.10 mg/kg of feed and 0.32 mg/kg of feed	Prior to and during egg laying	Diet	Chicken	Distribution to egg lower than that of diets containing an equal concentration of natural selenium	Latshaw (1975)
Sodium selenite	8 mg/kg of feed	During egg laying	Diet	White Leghorn chicken	Mercury altered the distribution of selenium in the egg	Magat and Sell 1979)
Sodium selenite	8 mg/kg of feed	During egg laying	Diet	White Leghorn chicken, Japanese quail	The level of Hg in the yolk of eggs was decreased by the addition of selenium to the diet	Sell (1977)

continued-

Table V-8 - continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Distribution to Fetus, Embryo, Egg	Reference
Sodium selenite	7.5 μg/rat	Daily injection from day 11 to 13 until day 18 to 20 of gestation (7 days)	Parenteral	Rats, Sprague-Dawley	Placental transmission was dose-dependent. Placental tissue always contained more selenium than the uterus and amniotic fluid. The concentration in the fetus was lower than all other tissues connected with reproduction	Rosenfeld (1964)
Selenium of undetermined form	2 mg/kg	Simultaneous with mercuric chloride	s.c.	Rats, Wister	Selenium decreased placental transport of mercuric chloride	Parizek et al. (1969)
Selenomethionine	Trace, 0.13 mg	5 min to 2 days	i.v.	Mice	Evidence of placental transmission by autoradiography	Hansson and Jacobsson (1966)
Sodium selenite	0.2 mg/kg	One injection on day 15 of gestation	s.c.	Mice (ICR)	Methylmercury causes a redistribution such that selenium is higher in the brain and the fetus. Selenium causes brain levels of mercury to increase and fetal mercury levels to decrease	Iijima et al. (1978)

continued-

Table V-8 - continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Distribution to Fetus, Embryo, Egg	Reference
Inorganic selenium	0.1 or 0.5 mg/kg of feed	Throughout gestation	Diet	Swine cross-bred	Levels of selenium in the serum, kidney and liver of neonatal swine reflected the level of inorganic selenium in the mother's diet. This reflects a dose-responsive placental transfer. The maternal and neonatal levels of selenium did not increase proportionally to doses above 1 mg/kg in the diet	Mahan et al. (1977)
Sodium selenite	1, 2 or 5 mg/day	Daily from 90 days prepartum through 6 to 7 months of lactation	In diet of adult	Hereford cows	Selenium levels in calves of dams fed 1 or 2 mg/day were not increased over controls; levels were increased over controls for those fed 5 mg/day	Perry et al. (1978)

transfer of selenium from the mother to the egg or to mammalian fetuses across the placenta. As was stated earlier, tissue concentrations of 6 to 18 mg/kg have been recorded in abnormal chicken embryos layed by hens on seleniferous feed (Poley et al. 1937). Other studies listed in Table V-8 show that natural selenium, presumably in the form of selenoamino acids, results in higher concentrations of selenium in the embryo and egg than does selenite (Latshaw 1975). This could mean that hens on seleniferous feeds could reach higher egg concentrations of selenium than those reported in studies using added selenite. It is also important that there are interactions of selenium with other metals which result in altered concentrations of selenium in the egg (Magat and Sell 1979, Sell 1977).

Placental transfer seems to be dose-dependent (Rosenfeld 1964). Mahan et al. (1977) indicated, however, that increasing the concentration of inorganic selenium in the diet of swines from 0.1 mg/kg to 0.5 mg/kg resulted in a disproportionately lower amount of selenium crossing the placenta. In addition, Rosenfeld (1964) has shown that, in the rat, doses of sodium selenite of 2 mg/kg resulted in a lower percentage of total selenium being transferred than did a lower dose. The fetus always contained a lower concentration of selenium than either the reproductive organs or the placenta.

We can conclude from the data presented in Tables V-7 and V-8 that relatively high doses of selenium are teratogenic to chickens and probably to other egg-laying animals and aquatic organisms. Mammals, however, even when given toxic doses, are not likely to show a high embryotoxic or teratogenic response. Mammals do sequester selenium at some stage of their gestation and respond to altered maternal concentrations by similar changes in the fetus. In addition, it seems probable that at near-toxic doses, which will ultimately affect reproductive performance of the adult, there may be a decrease in birthweight and viability of the young.

It should be pointed out that several organic selenium compounds are likely to cross the placenta more efficiently than selenite. More work on this source of selenium toxicity to mammalian fetuses needs to be done, especially in light of the case reports of teratogenicity to range animals on seleniferous feeds.

Table V-9 lists the documented interactions of selenium with mercury (methylmercury), arsenic (arsenate), and sulfur (sulfate). Iijima et al. (1978) and Parizek et al. (1969) have shown that mercuric chloride and methylmercury interact with selenium. Selenium competes with these compounds for transplacental passage, and its presence reduces methylmercury and mercuric chloride concentrations in the fetus. Conversely, selenium concentrations are reduced transplacentally by methylmercury and mercuric chloride. At selenite doses of 0.0625 to 0.25 mg Se/kg/day it produces a protective effect; however, at 0.5 to 1.0 mg Se/kg/day subcutaneously or 2 mg Se/L in the drinking water, it increases fetal resorptions. At 4 mg Se/L in the drinking water it decreases resorptions but increases the incidence of cleft palate. This is surprising in that selenite at 0.2 mg Se/kg subcutaneously causes a decrease in fetal levels of mercury (Iijima et al. 1978), and selenium apparently decreases placental transport of mercuric chloride (Parizek et al. 1969).

Table V-9. Teratology Influenced by Selenium Interactions with Other Chemicals.

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Teratogenic interaction with other chemicals	Reference
Sodium selenite	7.6 mg/kg-bw	Simultaneous injection with cadmium on the 21st day of gestation	s.c.	Rat Wistar Konarovice	Selenium prevented all teratogenic effects of cadmium.	Parizek et al. (1968)
Sodium selenite	2 mg/kg-bw	Injection simultaneously or within 30 min of cadmium or arsenate on day 8 of gestation	i.v.	Golden hamster (*Cricetus auratus*)	Cadmium sulfate 2 mg/kg-bw produced 51% abnormal fetuses, including encephalocoele, exencephaly, cleft palate, and microopthalmia. In addition, 22% of the fetuses died. Sodium selenite reduced these values to 4% and 2% respectively. Sodium arsenate at 20 mg/kg induced 49% malformations and 35% resorptions. Sodium selenite reduced these values to 19% and 20%, respectively.	Holmberg and Ferm (1969)
Sodium selenite	0.2 mg/kg-bw	One injection on day 15 of gestation	s.c.	Mice (ICR)	Methylmercury causes redistribution of selenium such that it is higher in the brain and fetus. Selenium causes brain levels of mercury to increase and fetal mercury levels to decrease.	Iijima et al. (1978)

continued-

Table V-9 - continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Teratogenic interaction with other chemicals	Reference
Sodium selenite	0.0625 to 3.5 mg/kg-bw	Daily on days 9 to 12 or 7 to 12 of gestation, simultaneously with methylmercury	s.c.	Mice (ICR) C57BL	High Se concentrations (0.5 and 1.0 mg/kg/day) potentiated fetal resorption, placental weight, and dead fetal weight caused by methylmercury; lower selenium concentrations (0.0625 to 0.25 mg/kg/day) had a protective effect.	Lee et al. (1979)
Sodium selenite	2 or 4 mg/L	30 days prior to gestation to day 18 of gestation	Drinking water	Mice (IVCS)	2 mg/L of selenium given with methylmercury increased resorptions caused by methylmercury, whereas 4 mg/L selenium given with the high methyl mercury dose decreased embryo mortality and increased the incidence of cleft palate	Nobunaga et al. (1979)
Sodium selenite	0.6 mg/kg/egg	One injection on day 14 of gestation	Air cell of egg	White Leghorn chicken	Potassium sulfate at 0.5 mg/kg increased embryo mortality over seleniumal one from 57% to 81%.	Halverson et al. (1965)

continued-

Table V-9 - continued

Compound	Dose or exposure	Duration of treatment	Route of treatment	Species & strain	Teratogenic interaction with other chemicals	Reference
Sodium selenite	0.3 mg/kg/egg	One injection on day 4 of incubaation	Air cell of egg	Chicken	0.1 mg/kg sodium arsenite increased LD_{50} of embryos exposed to sodium selenite and selenomethionine, but did not affect the LD_{50} of trimethyl selenonium chloride	Palmer et al. (1973)
Selenomethionine	0.13 mg/kg/egg	One injection on day 4 of incubation	Air cell of egg	Chicken		Palmer et al. (1973)
Trimethyl selenonium chloride	15.7 mg/kg/egg	One injection on day 4 of incubation	Air cell of egg	Chicken		Palmer et al. (1973)
Sodium selenite	8 mg/kg of feed	During egg laying	Diet	White Leghorn chicken, Japanese quail	The level of mercury in the yolk of eggs was decreased by the addition of selenium in the diet	Sell (1977)
Sodium selenite	8 mg/kg of feed	During egg laying	Diet	Chicken	Methylmercury, 20 mg/kg, in the diet reduced the level of selenium in the yolk and increased selenium in the white. The inverse relationship exists for the selenium effect on mercury distribution	Magat and Sell (1979)

Cadmium and arsenate, both of which are proven mammalian teratogens, are dramatically inhibited by selenite (Parizek et al. 1968, Holmberg and Ferm 1969). Potassium sulfate and sodium arsenite increase the embryotoxicity of selenium to chicken embryos (Halverson et al. 1965, Palmer et al 1973). These interactive effects serve to add further uncertainty to understanding the role of selenium as a potential teratogen in mammals.

F. Mutagenicity

Sentein (1967) studied the cytogenetic effects of copper selenate, selenium dioxide, and sodium and potassium selenates and selenites. Eggs of *Triturus helveticus* and *Pleurodeles waltlii* were treated *in vitro* during mitosis. Incubation of *Pleurodeles* eggs in a saturated (0.9 M) solution (pH 3.65) of copper selenate for 45 minutes produced effects similar to those seen with 0.01 M selenium dioxide: fatal destruction of fibrillar architecture and cytoskeleton, with pronounced toxicity as evidenced by egg cytolysis. Polar dissociation with prolonged dominance of the principal pole and stickiness and clumping of the chromosomes were observed. Copper selenate has similar effects on *Triturus* eggs. All effects were shown to be concentration-dependent, as lower concentrations (0.01 M) had much less pronounced effects. At 0.01 M, sodium and potassium selenates and selenites had no effect on mitosis, while at 0.1 M these salts all produced effects similar to those of copper selenate. Hence, the observed effects were attributed to selenium. Whether the effects resulted in other mutagenic changes was not indicated.

Ting and Walker (1969) studied crossing-over over the major part of the X chromosome of Drosophila melanogaster. Testcross progeny of y cv v f/++++ females were fed as larvae on media containing a logarithmic concentration series of selenocystine (control, 1.63, 5.22, 16.3, 81.6 µM) or selenomethionine (1.63, 5.22, 16.3 µM). Dose-dependent reduction in recombination was significant by analysis of variance in one of the two experiments with selenocystine and in the selenomethionine experiment. Double-crossover progeny, studied separately, showed a gradual overall drop in total frequency with doses from 1.63 µM to 81.6 µM in all experiments. This was accompanied by appreciable shifts in the relative densities of double-exchange events in the 3-segment pairs at intermediate concentrations, and a reverse shift to the 1.63 µM values at 81.6 µM. Analysis of these shifts indicated that relative initial attenuation of coincident crossovers was always least in y-cv; results were equivocal with regard to the relative attenuation in cv-v and v-f. The results were interpreted according to a polaron-hybrid DNA model, supporting the hypothesis that chromosomal protein, linearly associated with the DNA, mechanically induced breakage in the DNA. The finding that the treatment curves for single-exchange chromosomes showed considerable evidence for treatment effects with little effect on the frequency for the total segment remained unexplained.

Chapco et al. (1978) studied genetic and environmental interactions (GxE) at the intrachromosomal level (segments of the X-chromosome) in Drosophila melanogaster. Homozygous recombinant lines were mated and allowed to deposit their eggs on a medium supplemented with selenocystine (Se replacing S in cystine). For each genotype, the number of eggs deposited (on the sixth day post-eclosion) by singly-mated females was determined. Egg-to-adult viability was estimated by the percentage of eggs that resulted in adult flies. The results showed that selenocystine, in a dose-dependent manner, reduced fecundity for all genotypes, but not viability. In fact, viability was generally increased. It was concluded that the extent of an X-chromosome segment's effect on a trait is not paralleled by the extent of its association with the trait's sensitivity to chemical treatment. Further, the effects of selenocystine on egg production and egg viability are dependent on the genotype.

The effects of Na_2SeO_3 on the mutagenicity of 2-acetylaminofluorene (AAF), N-hydroxy-AAF (N-OH-AAF) and N-hydroxy-2-aminofluorene (N-OH-AF) were studied in the Ames Salmonella typhimurium (tester strain TA 1538) assay by Jacobs (1977). It was found that 10 to 40 mM Na_2SeO_3 reduced the mutagenicity of N-OH-AAF in a dose-dependent fashion when studied in the presence of rat liver 9000xg supernatant as an activating system. The same concentrations of Na_2SeO_3 were tested with AAF (in the presence of rat liver microsomes) and N-OH-AF (without activation). In both these latter cases, 22% to 47% inhibition of mutagenicity was observed, but no dependency on dose was demonstrated. The results of these experiments were also reported by Jacobs et al. (1977b).

Schut and Thorgeirsson (1979) studied the effect of Na_2SeO_3 on the mutagenic activation of N-OH-AAF (in Salmonella tester strain TA 1538) mediated by a 9000xg supernatant fraction prepared from epithelial cells of the rat small intestine. It was found that Na_2SeO_3 was not mutagenic in the absence of N-OH-AAF. Since these authors found that Na_2SeO_3 was very toxic to the bacteria, the results were expressed as revertants per 106 surviving bacteria. With a constant concentration of N-OH-AAF (7.5 ug/mL) and Na_2SeO_3 concentrations less than 0.6 mM, the number of revertants/106 survivors was independent of the Na_2SeO_3 concentration. At 0.8 to 2.0 mM Na_2SeO_3, when 67% to 94% of the bacteria were killed, Na_2SeO_3 enhanced the mutagenicity of N-OH-AAF in a dose-dependent fashion. This effect, which opposed the findings of Jacobs (1977), was believed to be due to the antioxidant properties of Na_2SeO_3.

Noda et al. (1979) studied the mutagenicity of Na_2SeO_4 and Na_2SeO_3 in both the _Bacillus_ _subtilis_ _rec_$^{+-}$ assay and in the Ames _Salmonella_ system. In the _Bacillus_ assay, both Na_2SeO_3 (7.82 to 62.5 mM) and Na_2SeO_4 (31.25 to 250 mM) showed slight DNA-modifying activities as evidenced by the differences in the length of zones of growth inhibition between the H17 (rec^+) and M45 (rec^-) strains. At the lower concentrations Na_2SeO_3 showed a higher DNA-modifying activity than Na_2SeO_4. In the _Salmonella_ assay, both salts were mutagenic in strain TA 100, with Na_2SeO_3 exhibiting the higher number of revertants per plate at the lower concentrations tested (2 to 3 umoles/plate). Neither Na_2SeO_4, nor Na_2SeO_3 was mutagenic in strains TA 98 or TA 1537. The results obtained by these authors with the _Bacillus_ assay oppose those of Nishioka (1975) who reported that 2.5 umoles of Na_2SeO_4 or Na_2SeO_3 did not show any DNA-modifying activity in the _Bacillus_ _rec_$^{+-}$ assay. Noda et al. (1979) attributed this discrepancy to the different concentrations tested in the two studies.

Shamberger et al. (1979) studied the effects of Na_2SeO_3 on the mutagenicity of the direct-acting (i.e. not requiring metabolic activation) mutagens malonaldehyde (41.6 μmoles/plate) and β-propiolactone (1.18 mmole/plate) in several Salmonella test strains. At 0.0067, 0.067 and 0.67 μmoles/plate, Na_2SeO_3 reduced the mutagenicity of malonaldehyde in strains TA 1975 (base-pair substitution sensitive) and in TA 1977 and TA 1978 (both frameshift sensitive). Effects of Na_2SeO_3 in the other strains (His G46, His C207, His C3076 and His D3052) were absent or very minimal. No statistical analysis was performed nor was the toxicity of Na_2SeO_3 to the bacteria studied. Na_2SeO_3 reduced the mutagenicity of β-propiolactone in all strains, except in His D3052 and in His G46. However, with neither one of the two mutagens tested was a clear dose-response of the effect of Na_2SeO_3 demonstrated; maximum inhibitory effects were seen at both the highest (0.67 μmoles/plate) and lowest (0.0067 μmoles/plate) concentrations of Na_2SeO_3 tested.

Whiting et al. (1980) used cultured Chinese hamster ovary cells to study the effect of a sulfhydryl reducing agent, glutathione, on the frequency of chromosome aberrations caused by treatment of the cells for three hours with Na_2SeO_3 or Na_2SeO_4. Na_2SeO_3 induced chromosome aberrations (breaks and exchanges) both in the presence and in the absence of glutathione. With Na_2SeO_3 alone, no effect was seen at concentrations from 10^{-6} M to 5 x 10^{-5} M, while significant aberrations (in 7% to 10.5% of the cells) were seen at 1 to 2 x 10^{-4} M Na_2SeO_3. In the presence of 10^{-4} M glutathione, significant increases in the frequency of aberrations occurred (6.8% to 13.0% of the cells) at 2 x 10^{-5}M Na_2SeO_3. The addition of glutathione resulted in a considerable increase in cytoxicity and inhibition of mitotic activity. Increased frequencies of aberrations were observed with Na_2SeO_4 alone (up to 6.5% of the cells at 2×10^{-3} M) and Na_2SeO_4 plus 10^{-4} glutathione (16.3% at 2×10^{-3} M). Higher concentrations of Na_2SeO_4 inhibited mitosis. Glutathione (10^{-3} M) in the presence of Na_2SeO_4 resulted in an extent of toxicity equal to that observed with a tenfold higher concentration of Na_2SeO_4 alone and the levels of aberrations were near control values. The addition of 10^{-2} M glutathione neither enhanced the toxicity of selenate, nor altered the frequency of aberrations when compared to that observed with Na_2SeO_4 alone.

The data concerning mutagenicity of selenium is inconclusive. In some systems, selenium elicits mutagenic properties while in others, it has no effect.

G. Carcinogenicity and Anticarcinogenicity

1. Carcinogenicity

Since the 1940s, numerous research studies have demonstrated the toxicity of organic and inorganic selenium compounds to humans and domestic and laboratory animals. Most of the toxicity studies have investigated the acute and chronic effects of selenium for up to two years exposure. These studies failed to demonstrate a significant increase in malignant tumor rates among the selenium-exposed animals versus unexposed controls. Only six long-term toxicologic investigations provide information concerning the carcinogenic potential of selenium compounds. These studies are summarized below:

Nelson et al. (1943) fed rats 5, 7 or 10 μg selenium/g of diet for 2 years. A total of 126 rats were exposed to selenium and 18 served as controls. Of 51 rats that survived (39 treated and 12 controls) at least 24 months, 11 developed liver tumors diagnosed as hepatic cell adenomas or low grade hepatic cell carcinomas. Four others had pronounced adenomatoid hepatic cell hyperplasias that could be interpreted as a transition to tumor. In the 73 selenium-treated rats that died or were sacrificed before 18 months, there were no tumors and no advanced adenomatoid hyperplasia, although cirrhosis was frequent (after three months). The 14 control rats that lived at least 18 months had neither adenomatous, nor neoplastic lesions or cirrhosis. The spontaneous incidence of hepatic tumors in the colony (source of control animals) at that time was 0% in rats less than 18-months old, 0.5% in rats 18 to 24-months old, and 0.9% in rats finishing a two-year experimental or control period. None of the tumors in the test animals had metastasized and there was no associated hepatic cirrhosis.

Histological examinations revealed that portions of the peripheries of the tumors were separated from the rest of the liver by collagenous fibers, but there was no complete encapsulation. The growths were composed of fairly regular to irregular cords of large hepatic cells, usually more oxyphilic than the surrounding liver in the adenomas and less oxyphilic in the carcinomas. Moderate numbers of mitosis were in some tumors while none occurred in others.

Bile duct proliferation was slight. Hemosiderin pigment and fibrosis within the tumors was insignificant and focal necrosis was rarely seen. Fatty degeneration was slight and was similar for both selenium-treated and control rats. A few of the tumors enclosed small foci of myeloid cells, and in a few there were small cystic areas.

The authors indicated that differentiation between adenoma and low-grade carcinoma was difficult since the latter showed greater irregularity of liver cell cords, decreased oxyphilia of liver cells, more mitotic figures, and an invasive tendency at their margins.

In two other studies (Harr et al. 1967, Tinsley et al. 1967) a total of 1,437 Wistar rats from the University-maintained colony were assigned to 34 different dietary groups. Selenium levels ranged from 0.5 to 16 ug/g as dietary sodium selenite and sodium selenate in animals maintained on high and low protein basal rations (22% casein, 12% casein, and 12% casein plus 0.3% DL-methionine). The sodium selenite and sodium selenate were spectroscopically pure. Both male and female rats were included in the experiment, but the number of each assigned to the individual dietary groups was not reported. The age of the animals at the time of initial exposure was also not reported, but, with the exception of 136 animals that were killed at specific ages, all animals were maintained until moribund, at which time they were sacrificed, or until death. Since the primary purpose of the study was to evaluate the carcinogenic potential of selenium, a suspected hepatocarcinogen, N-2-fluorenyl-acetamide (FAA), was fed at dietary levels of 100 and 50 ug/g to establish the index of carcinogenesis in the colony. Nine of the dietary groups with a total of 290 animals were used in complementary experiments to test such features as exposure to multiple dose levels, intermittent exposures and limited feed intake.

Due to excessive losses in the high-selenium groups (16 μg/g selenite and 22% casein; 16 μg/g selenate and 22% casein; and 8 μg/g selenate and 12% casein), the animals in these groups were sacrificed early. One hundred seventy-five rats lived two years or more. The rats on the control diets showed no evidence of malnutrition. The hepatic changes of the older animals included accentuated lobular pattern, hyperemia, cellular degeneration, mildly proliferative hepatocytes, binucleation, and multiple nucleoli.

Eleven hundred twenty-six out of the original 1,437 animals were autopsied. Acute toxic hepatitis was generally observed in animals receiving selenium added to the semipurified diets at the rate of 4, 6, 8 or 16 μg/g and in the commercial diet with 16 μg/g of added selenium. Animals with acute toxic hepatitis lived less than 100 days. Some of the animals suffered from chronic toxic hepatitis. Hyperplastic lesions predominated in the livers of about 50% of the selenium-fed animals that lived more than 282 days. Gross pathology revealed these lesions were similar to those with chronic toxic hepatitis.

Sixty-three neoplasms were found in the study although only 62 were listed in the author's date table (Table V-10). Forty-three occurred in the

Table V-10. Distribution of Neoplasms in Rats on Experimental Diets.[a]

Diet		No. Necropsies	Neoplasms				
					Age (days)		
Type	Selenium (µg/g)		No.	Type	Low	Medium	High
Selenite with 22% casein	0.5	49	1	Uterine polyp	–	752	–
			11	Lipoma	–	450	–
	2.0	47	1	Mammary cancer	–	174	–
	6.0, 8.0, 16.0	65	–[b]	–	–	–	–
Selenate with 22% casein	0.5	44	1	Uterine cancer	–	380	–
	2.0	41	1	Lymphoma	–	563	–
			1	Fibroma	–	500	–
	8.0	37	1	Urinary cancer	–	43	–
	4.0, 6.0, 16.0	54	–	–	–	–	–
Selenate with 12% casein	0.5	47	1	Mammary cancer	–	722	–
			1	Lymphoma	–	730	–
	2.0, 4.0, 6.0, 8.0	103	–	–	–	–	–
Selenate with methionine	4.0	38	–	–	–	–	–
	6.0	13	–	–	–	–	–
	8.0	15	–	–	–	–	–
FAA 100 ug/g 22% casein	0	45	12	Hepatic cancer	243	313	512
			7	Mammary cancer	243	308	578
			3	Lymphoma	154	247	282

continued-

---

[a] From Harr et al. (1967)

[b] – = Data not specified

Table V-10 - continued

Diet		No.	Neoplasms				
					Age (days)		
Type	Selenium (µg/g)	Necropsies	No.	Type	Low	Medium	High
FAA 50 µg/g 12% casein	0	43	14	Hepatic cancer	299	402	689
		-	4	Mammary cancer	296	318	412
		-	2	Fibroma	282	-	309
		-	1	Bile duct cancer	-	418	-
Controls:							
12% casein	0	98	3	Mammary cancer	92	548	707
			1	Lymphoma	-	356	-
			1	Lipoma	-	731	-
22% casein	0	103	3	Mammary cancer	620	678	731
			1	Fibroma	-	458	-
12% casein 0.3% DL-methionine	0	29	1	Broncho cancer	-	434	-
Commercial diet	-	46	1	Lymphoma	-	578	-
Variable selenium and control diets	-	206	-	-	-	-	-

88 rats fed FAA. The other 20 were randomly distributed through the experimental diets and included no hepatic neoplasms.

Thus, although lifetime exposures to toxic levels of selenium were found by these workers to produce both necrotic and hyperplastic changes in the liver and other organs of the rats, no hepatic cancers were observed among the selenium-exposed animals. The total number of cancers and the site distribution were similar to those observed in controls. Harr et al. (1967) concluded that neoplasia in the rat is not induced by selenite, selenate, or methionine and selenate combined.

Scott (1973) provided some discussion concerning the potential causes for the differences in results observed by Nelson et al. (1943) and Harr et al. (1967). Based on the available information, it is impossible to determine conclusively the causes for the differences; however, some of the possible explanations are: (1) different strains of rats were used in the two studies, (2) the form of selenium exposure differed and (3) degree of lesions varied between the two studies.

Cherkes et al. (1962) and Volgarev and Tscherkes (1967), in a series of three experiments, fed selenium as sodium selenate to 200 heterozygous rats at the rate of 4.3 or 8.6 μg Se/g of feed. The feeds were not semipurified. They contained 12% to 30% casein with additions of riboflavin, methionine, α-tocopherol, cystine, nicotinic acid, and choline in appropriate groups. In the third trial, a set of 200 control rats were fed a stock diet and observed for a longer period of time than the experimental rats.

In the first series (Table V-11), 40 rats were fed 4.3 ug Se/g of diet as sodium selenate plus 12% casein for periods of up to 36 months. No indication was given as to the age or weight of the animals at the start of the experiment, but it is assumed that weanling rats were used. In the 23 rats surviving 18 months or longer, 10 developed tumors and 4 had precancerous lesions. No information was given concerning the 17 rats that died prior to 18 months. Of the 10 rats with tumors, 3 developed hepatic carcinomas (2 with metastases to the lungs), 3 had hepatocellular adenomas, and 4 developed sarcomas. Of the 13 noncancerous rats, 4 had precancerous lesions including cholangiofibrosis, oval cell (bile duct cell) proliferation, and biliary cysts. There was no indication as to when the tumors appeared other than the statement that they were seen some time after the 18th month. No control rats were included in this series.

In the second series (Table V-11), 60 male rats, divided into three groups of 20, were fed 4.3 ug Se/g of a 12% casein diet for six months. Group 1 was maintained on 12% casein, but the level of selenium was increased to 8.6 ug Se/g of diet commencing with the seventh month. Group 2 was fed 8.6 ug Se/g of diet and the casein level of the diet was raised to 30%. Group 3 received the same diet as Group 2 with the addition of riboflavin. Protein levels in Groups 2 and 3 were increased to 30% to prevent possible death losses from the increased selenium levels.

Eighteen of the original 20 rats assigned to Group 1 survived to the end of the initial six-month period. However, all 18 died within the next six

Table V-11. Summary of Experimental Results on Selenium Carcinogenesis.[a]

Series and group	Diet	No. of animals	Pathology Liver cancer	Liver adenoma	Liver pre-cancer	Sarcoma	Total
I							
1.	12% casein; 4.3 ug/g Se	40	3	3	4	4	14
II							
1.	12% casein 8.6 ug/g Se	20[b]	-	-	-	-	-
2.	30% casein; 8.6 ug/g Se	20	1	0	0	2	3
3.	30% casein; 8.6 ug/g Se plus riboflavin	20[c]	0	1	0	1	2
III							
1.	12% casein; 4.3 ug/g Se	20[d]	0	0	0	0	0
2.	12% casein; 4.3 ug/g Se plus methionine and α-tocopherol	20	0	0	0	0	0
3.	12% casein; 4.3 ug/g Se plus cystine	20[e]	0	0	0	0	0
4.	12% casein; 4.3 ug/g Se plus nicotinic acid	20	0	0	0	0	0
5.	12% casein; 4.3 ug/g Se plus choline	20	0	0	0	0	0
	Totals	200	4	4	4	7	19

[a] Adapted from Volgarev and Tscherkes (1967)
[b] All died during first year
[c] During first year 17 of 20 rats died
[d] All rats died by 26 months
[e] Sacrificed 17 months

months following the increase of selenium to 8.6 μg Se/g of diet. Microscopic examinations revealed the characteristic histologic changes of selenium intoxication. There were no cancerous or precancerous changes in the liver.

Seventeen of the original 20 rats assigned to Group 2 were surviving at the end of the initial six-month period. Increasing the dietary selenium from 4.3 μg Se/g to 8.6 μg Se/g appeared to have no effect on survival of this group, since 16 animals still remained at the end of one year and 12 lived more than two years. These results suggest that increasing the casein in the diet from 12% to 30% at the end of six months had a protective effect. At 14 months, sarcomas were found in two rats, one of the mediastinum, the other of the mesenteric lymph nodes. A third rat had liver cirrhosis with multiple nodules. No precancerous lesions similar to those in the first series were found. The rats examined after one-year of exposure showed changes characteristic of chronic selenium poisoning. Degenerative and atrophic changes in the liver and spleen were observed in rats surviving two years.

Seventeen of the 20 rats assigned to Group 3 died within the first year. Of the three rats surviving more than one year, one developed a sarcoma in a mesenteric lymph node that was found at 19 months, another had hyperplasia of the liver cells with some nodules of hepatocellular adenoma, and the third rat had only degenerative changes in visceral organs.

In the third series (Table V-11), 100 heterozygous male rats each weighing 100 g were allocated into five groups of 20 animals each and placed on a basal diet containing 12% casein and 4.3 μg Se/g as sodium selenate.

Additives were included in the group diets in order to test their effects on the development of possible selenium-induced carcinogenesis. The assignment of dietary additives was as follows:

Group 1: no additives

Group 2: methionine at 5,000 μg/g and α-tocopherol at 10,000 μg/g

Group 3: cystine at 5,000 μg/g

Group 4: nicotinic acid at 5 mg per rat per day

Group 5: choline at 35 mg per rat per day

All of the rats in Group 1 were dead by the 26th month, 10 months earlier than similarly fed animals in series I. The animals in Groups 2, 4 and 5 were sacrificed at the end of the 25th month and those in Group 3 at the end of the 17th month. None of the animals had tumors or precancerous lesions. No spontaneous tumors were observed in the 200 heterozygous male control rats fed stock ration.

Volgarev and Tscherkes (1967) have suggested that the reason for the difference in tumor rates between the series I and series III experiments may be that the experiments of series III were started two years after series I and involved animals obtained from a different source. They note, however, that of 10,000 other rats used in their laboratory, not a single case of spontaneous liver cancer was seen. No information was provided concerning the examination methods, exposures, rat strains, etc., for the 10,000 rats.

In two other studies (Schroeder 1967, Schroeder and Mitchener 1971a, 1972), 418 weanling rats of the Long-Evans strain, BLU: (LE), born from random-bred females (purchased from Blue Spruce Farms, Altamont, NY) were fed a diet of whole rye flour (60%), dry skim milk (30%), corn oil (9%), and iodized sodium chloride (1%), to which were added vitamins and iron. The diet contained approximately 24% protein, 65% carbohydrate, and 11% fat on a dry basis, at 396 kcal/100 g. Selenium content of the diet was 0.05 µg/g, wet weight. The rats were divided into four groups of approximately 100 animals each. One group served as a control, and the second, third, and fourth groups received 2 to 3 mg/L of sodium selenate, 2 to 3 mg/L of sodium selenite, and 2 mg/L of sodium tellurite, respectively, in the drinking water. Within a group, the results were reported separately by sex. Because selenite was very toxic to male rats, causing 50% mortality in 58 days, sodium selenate was substituted at 2 mg/L until one year of age when the level was raised to 3 mg/L. There were no significant differences in the weights of male rats fed selenate and their controls at any interval up to 36 months of age. Since selenite was not as toxic for females (50% mortality at 348 days), sodium selenate was not substituted for selenite and the dose level was maintained at 3 mg/L.

When the rats were 21 months old, an epidemic of pneumonia struck the colony with considerable loss of life. It was controlled with penicillin in the drinking water in about three weeks. Losses in the various groups were: male controls, 36.5%; male selenate, 48.9%; female controls, 27.2%; female selenate, 14.8%.

The average weights of the male and female groups of selenate-supplemented rats were not significantly different from the controls during the 36-month experiment. In contrast, selenite-fed females showed significant depressions of weight relative to the controls at all 6-month intervals, except at 18 months. As mentioned above, sodium selenite was highly toxic to male rats.

Approximately 75% of the control and selenate animals living prior to the epidemic of pneumonia at 28 months were autopsied. Histological examinations were performed on 65 control and 48 selenate-exposed rats. The criteria used to select animals for autopsy or histologic examination were not reported. Also, the ages of the animals at autopsy was not provided. Eleven malignant tumors were found in the control animals and 20 were reported in the selenate-supplemented animals. The types and numbers of tumors reported are shown in Table V-12.

The anatomical locations of the sarcomas and pleomorphic carcinomas were not reported. Histologic slides were prepared only from selected organs and animals, and the rationale for that selection was not reported. Since the organs and tissues were not systematically searched, type and incidence of histologic lesions are not known (NAS 1976). Types and numbers of tumors within groups were not reported according to sex. Schroeder and Mitchener (1971a, 1972) concluded that selenate was carcinogenic for Long-Evans rats.

Malignant tumors in the selenite-fed rats included a reticulum cell sarcoma and three spindle cell sarcomas invading the heart. Very little

Table V-12. Tumors in Rats Fed a Selenate-Supplemented Diet.[a]

Type	Control group	Selenate group
Mammary adenocarcinomas and fibrosarcomas	5	3
Spindle cell sarcoma	2	4
Leukemia types	2	4
Pleomorphic carcinoma	1	2
Leiomyosarcoma	1	0
Malignant hamartomas	0	2
Undifferentiated sarcoma	0	1
Round cell sarcoma	0	1
Malignant glioma	0	1
Ovarian adenocarcinoma	0	1
Spindle cell sarcoma invading the heart	0	1
Totals	11	20

---

[a] From Schroeder (1967) and Schroeder and Mitchener (1971a, 1972)

malignant tumor information was given concerning the male and female groups initially fed selenite. Due to the toxicity of selenite, the exposure for males was changed to selenate and both groups were sacrificed prior to the age of high tumor incidence.

Schroeder and Mitchener (1972) repeated the rat studies in mice. Treatment with 3 mg Se/L, as either sodium selenite or sodium selenate in the drinking water, did not have a significant effect on the incidence of spontaneous tumors.

The National Cancer Institute (1980) carried out a chronic bioassay on selenium disulfide in six-week old male and female mice and rats by gavage. The protocol for the chronic bioassay is described below:

Four groups (per sex) of 50 six-week old B6C3F1 mice were used in the bioassay. The four groups for each sex were defined as follows: untreated control (animals were kept in the same environment and fed a similar diet to treated animals but did not receive anything by gavage); vehicle control (animals were kept in the same environment and fed a diet similar to treated animals but received the vehicle carboxymethyl cellulose by gavage); low-dose test (20 mg/kg-bw selenium sulfide or 11.05 mg/kg-bw selenium); and high-dose test (100 mg/kg-bw selenium sulfide or 55.24 mg/kg-bw selenium). Oral administration was initiated about two months after birth and continued once daily for the remainder of life (up to 728 days).

Four groups (per sex) of 50 six-week old F344 rats were included in the bioassay. Untreated controls and vehicle controls were maintained as for the mouse study. Low-dose test rats were given 3 mg/kg-bw selenium sulfide (or 1.65 mg/kg-bw selenium) by gavage; the high-dose rats received 15 mg/kg-bw selenium sulfide (or 8.29 mg/kg-bw selenium). The vehicle was carboxymethyl cellulose. Oral administration continued once daily throughout the lifetime of the animals (up to 728 days).

The significant effects that could be related to the oral administration of selenium sulfide at the doses used were: decreased body weight and increased tumor formation in female mice and in rats of both sexes. Dosed rats and female mice had an increased incidence of hepatocellular carcinomas and adenomas. Dosed female mice also had an increased incidence of alveolar/bronchiolar carcinomas and adenomas.

The study concluded that selenium disulfide was carcinogenic for F344 rats and female B6C3F1 mice, inducing hepatocellular carcinomas in male and female rats and female mice and alveolar/bronchiolar carcinomas and adenomas in female mice. Selenium sulfide was not carcinogenic for male mice, but they were not able to tolerate the higher doses.

However, since selenium sulfide is not just another salt of selenium, but is instead a separate and distinct compound, it cannot be assumed that these results show that inorganic selenium (selenite or selenate) compounds are carcinogenic.

From the studies cited, it is apparent that the question concerning carcinogenicity of inorganic selenium remains questionable since recent information suggests selenium has anticarcinogenic properties (see following section, Anticarcinogenicity). Sufficient research has been completed to raise the possibility that inorganic selenium is a carcinogen, but none of the present studies produces evidence or conclusive dose-response data for risk estimation. The Commissioner of the Food and Drug Administration has concluded that: (1) the available information does not support classification of selenium or its compounds as having carcinogenic activity and (2) the use of selenium as set forth by the Food and Drug Administration regulations constitutes no carcinogenic risk (FDA 1974).

The conclusion of the (NAS 1976) is that despite an initial report of selenium as a carcinogen (Nelson et al. 1943), subsequent investigations demonstrated that chronic experimental exposure of rats and mice to selenium salts has not induced neoplasia (Cherkes et al. 1962, Harr et al. 1967, Nelson et al. 1943, Schroeder 1967, Schroeder and Mitchener 1971a, 1972, Tinsley et al. 1967, Volgarev and Tscherkes 1967).

The conclusion of the International Agency for Research on Cancer (IARC 1975) is that the available animal data are insufficient to allow an evaluation of the carcinogenicity of selenium compounds.

There does not appear to be adequate data to determine that selenium compounds are carcinogenic. The inability to demonstrate conclusively the carcinogenic potential of selenium compounds may be related to the insensitivity of the animal bioassays.

2. Anticarcinogenicity

Recently it has been shown that selenium supplementation has resulted in significant inhibition of both chemical and virus induced neoplasia (Medina et al. 1981, Harbach and Swenberg 1981, Besbris et al. 1982, Griffin and Jacobs 1977, Jacobs et al. 1977, Thompson and Becci 1980, Banner et al. 1982, Medina and Shepard 1981). It has been postulated that selenium inhibits the promotion phases of carcinogenesis. Upon withdrawal of the selenium supplement, tumors will emerge at the same rate as those in selenium untreated animals (Medina et al. 1981, Thompson and Becci 1980, Shamberger 1970, Griffin 1979, Souiller et al. 1981). In a report which demonstrated that selenium supplementation inhibited the induction of both chemical and virus induced tumors, it was observed that the development of preneoplastic lesions was very sensitive to selenium mediated inhibition (Medina and Shepard 1981).

It has been suggested that selenium protects against oncogenesis by inhibiting metabolic activation of the carcinogen (Daoud and Griffin 1978, Marshall et al. 1979). However, data from a recent study (Banner et al. 1982) indicated that the effect of selenium on carcinogenesis is probably due to a mechanism other than interference with carcinogen activation and interaction with cellular macromolecules. Another study (Clement 1981) concluded that selenium can inhibit both the initation and promotion phases of carcinogenesis and that a continuous intake of selenium is necessary to achieve maximum inhibition of tumor genesis.

Animal data on the anticarcinogenic effects of selenium compounds were summarized by the National Academy of Sciences (NAS 1976) and by Griffin (1979). There have been additional publications on the topic. Data from these investigations are summarized below.

a. Skin Tumors

Shamberger (1970) investigated the effects of selenium on the induction of skin papillomas and cancers in female ICR Swiss mice with 7,12-dimethylbenz(a)anthracene (DMBA). In nondietary tumor promotion experiments, 30 mice per group were treated once on day 1 with 0.125 mg of DMBA dissolved in acetone (DMBA was painted on the shaved backs of the mice). In one type of tumor promotion experiment, the shaved backs of the mice were treated on days 2 through 21 with 0.25 mL of a mixture of 20:80 water-acetone containing 0.0005% sodium selenide. In the second type of tumor promotion experiment, the mice were not treated with sodium selenide until three weeks after DMBA administration. Finally, in dietary experiments, the mice were fed torula yeast diets containing 0, 0.1 and 1.0 μg/g added sodium selenite for two weeks prior to a single application of 0.125 mg DMBA to the skin, or repeated daily applications for 27 weeks of 0.25 mL of 0.03% benzo(a)pyrene to the skin.

In five of six nondietary tumor promotion experiments, sodium selenide significantly ($P<0.05$) reduced the number of DMBA-induced papillomas in mouse skin. Torula yeast diets containing 1.0 μg/g sodium selenite markedly decreased the number of skin tumors induced by both DMBA and benzo(a)pyrene. Torula diets containing 0.1 μg/g sodium selenite did not decrease the tumor incidence.

b. Liver Tumors

An early study demonstrating the anticarcinogenic properties of selenium in chemically-induced liver cancer was carried out by Clayton and Baumann (1949). In this study, adult rats were maintained on semisynthetic diets and were given 0.064% of the dye 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) for four weeks. The animals were then fed the dye-free diet supplemented with 5 μg/g sodium selenite for four weeks. The basal diet containing the 3'-MeDAB was then fed for four more weeks, after which the dye free diet was fed for eight weeks. The animals were killed for examination. In two separate experiments, there was an approximately a 50% reduction in the liver tumor incidence for sodium selenite-fed animals as compared to control animals that received the basal diet during the second four-week period.

Marshall et al. (1979) reported the effect of sodium selenite administered in drinking water on the induction of hepatic tumors with 2-acetylaminofluorene (AAF). Male Sprague-Dawley rats weighing 200 g were allowed access to drinking water with 4 mg Se/L as sodium selenite for one week prior to carcinogen exposure. Two groups of rats received AAF at 0.03% for 14 weeks followed by 5 weeks of AAF-free diet. At the end of this time, the animals were sacrificed and the livers evaluated for tumor involvement.

Liver tumors were observed in 9 of the 13 surviving rats given the basal diet containing 0.03% AAF, whereas only 4 of the 14 rats in the selenium-supplemented AAF group had tumors.

Daoud and Griffin (1980) reported the effect of sodium selenite administered in drinking water on the induction of hepatic tumors with 0.05% 3'-MeDAB. This experiment was similar to the earlier study of Clayton and Baumann (1949). Groups of Sprague-Dawley rats were maintained *ad libitum* on a basal diet containing 0.05% 3'-MeDAB for nine weeks. Four of the groups also received sodium selenite in the drinking water according to the following regimens: (1) one group was given 4 mg/L selenium for the entire 9 weeks; (2) a second group was given 4 mg/L selenium for the initial 3 weeks; (3) a third group was given 4 mg/L selenium for the final 4.5 weeks; and (4) a fourth group received 2 mg/L selenium for the entire 9 weeks of study. After 9 weeks the animals were sacrificed and the livers examined for the presence of tumors. Supplementation of the drinking water with selenium afforded protection or slowed the rate of azo-dye hepatocarcinogenesis. The addition of 4 mg/L selenium to the water for the entire nine-week period reduced the final tumor incidence from 90%, in the control groups to approximately 15%. Selenium supplementation for the initial three weeks of the azo-dye administration also afforded some protection, while a somewhat lesser inhibition accompanied administration of selenium at later stages. Finally, the reduction of the selenium concentration to 2 mg/L provided less protection than was noted at the 4 mg/L level.

c. Liver and Mammary Tumors

Harr et al. (1972, 1973) fed selenium-depleted OSU-Brown rats a semipurified feed containing the hepatic carcinogen FAA (150 μg/g of feed), and 0.1, 0.5 or 2.5 μg Se/g added as selenite for 200 days. The incidence of mammary and hepatic neoplasia in animals without selenium or with 0.1 μg/g of added selenium was significantly higher than the incidence in rats supplemented with 0.5 or 2.5 μg/g of added selenium. One-half of the animals in the low selenium groups (0 and 0.1 μg/g) died before 200 days of age and had a 90% incidence of neoplasia. At this time, 5% of the rats fed 0.5 and 2.5 μg/g selenium had died and no subcutaneous neoplasms were observed. Most of the remaining rats fed 0.5 and 2.5 μg/g of selenium lived for an additional 120 days with the total incidence of neoplasia was 80% to 90%. Since the longevity of the rats was proportional to the amount of selenium supplementation and the duration of exposure to the carcinogen, the increase in cancer in the rats heavily supplemented with selenium may have been due to the greater exposure to the carcinogen or to the longer time for induction.

The mammary tumors in the group not supplemented with selenium were more invasive than those in rats from the three supplemented groups and predominated in the pelvic region. In contrast, mammary tumors in both the selenium-supplemented and control groups (commercial-diet fed rats) predominated in the thoracic region.

Three investigations by Schrauzer and co-workers have demonstrated the anticarcinogenic effects of selenium on the incidence of mammary adenocarcinomas in mice. In the first study (Schrauzer and Ishmael 1974), virgin C_3H/St mice, known to develop mammary adenocarcinomas with 85% incidence at the age of 12 to 16 months, were given 2 mg/L selenium in the form of selenite in the drinking water for 15 months. This exposure lowered the incidence of spontaneous mammary tumors from 82% (in untreated controls) to 10%.

In a second study (Schrauzer et al. 1976), the spontaneous mammary tumor incidence was determined in C_3H/St mice given 2, 5 or 15 mg/L selenium in the form of selenite in the drinking water; 10 or 80 mg/L arsenic in the form of arsenite in the drinking water; or a selenium/zinc supplement at the ratio of 5:200 mg/L. The tumor incidence in the 2, 5, and 15 mg/L selenium groups was 10%, 36% and 33%, respectively; the incidence in the 10 and 80 mg/L arsenic-treated groups was 27% and 40%, respectively; the incidence in the selenium/zinc group was listed at 94%. The selenium/zinc group incidence was similar to the 82% observed in the nontreated control groups of Schrauzer and Ishmael (1974). The investigators suggested that arsenic and zinc may function as selenium antagonists, thus accounting for the higher tumor incidences found in these studies. In a subsequent study, Schrauzer et al. (1978) reported that the joint administration of 2 mg/L arsenic as arsenite and of 2 mg/L selenium as selenite in the drinking water of inbred female C_3H/St mice increased the incidence of spontaneous mammary adenocarcinoma significantly over the untreated controls and animals receiving 2 mg/L arsenic or 2 mg/L selenium alone. These data indicated that arsenic counteracts the anticarcinogenic effects of selenium.

In this third study, Schrauzer et al. (1978) tested whether lower doses of selenium than were used in their previous studies would also reduce the occurrence of spontaneous mammary adenocarcinomas in C_3H/St mice. One group of 30 animals received selenium at a concentration of 0.45 ug/g of feed in a diet containing fishmeal as the main source of protein. Three other groups (27 to 30 mice per group) were fed the selenium-supplemented diet and also received selenium as selenite in the drinking water at concentrations of 0.1, 0.5 or 1 mg/L. The incidence of mammary tumors in these groups was recorded over a period of 24 months. The tumor incidence in the group fed 0.45 ug/g selenium in the diet was 42%, considerably lower than the 80% to 100% tumor incidence in the first study (Schrauzer and Ishmael 1974) in which the diet was not supplemented with selenium. The tumor incidence declined further to 25%, 19% and 10% with 0.1, 0.5, and 1.0 mg/L, respectively, of selenium in the drinking water. Selenium-supplemented groups also remained tumor-free for longer periods than the unsupplemented controls.

Thompson and Becci (1980) reported the effect of supplemental dietary selenium on the post-initiation state of mammary tumors induced by N-methyl-N-nitrosourea (MNU) in non-inbred female Sprague-Dawley rats. At fifty days of age, the rats were given an intravenous injection of either 0.9 percent NaCl or 50 mg MNU/kg-bw. Seven days after the injection, the rats were randomized into 2 groups of 25 rats each and fed laboratory chow containing either 0.5 or 5.0 mg Se/kg of diet. Selenium was provided as sodium selenite. The study was terminated 90 days after the carcinogen treatment. The tumor data indicated that the feeding of selenium prolonged the latency of mammary cancer appearance and resulted in a significant ($P<0.05$) reduction of the average number of mammary adenocarcinomas per rat.

d. Colon Tumors

Jacobs et al. (1977a) studied the effect of 4 mg Se/L administered as sodium selenite in drinking water on the incidence of colon cancers in Sprague-Dawley rats induced by DMH (1,2-dimethylhydrazine) or MAM (methylazoxymethanol acetate). Rats receiving DMH and no selenium exhibited an 87% tumor incidence (13 of 15 rats had tumors). Selenium significantly ($P<0.025$) decreased the incidence of colon tumors induced by DMH such that only 6 out of 15 rats had tumors. No significant difference in tumor incidence was apparent between groups receiving MAM with or without selenium supplements.

e. Lung Tumors

Thompson and Becci (1979) conducted an investigation to determine the effect of dietary selenium on the induction of tracheal cancer by 1-methyl-1-nitrosourea (MNU). Seven-week old male Syrian golden hamsters received intratracheal instillations of a 0.5% MNU solution once weekly for 12 weeks. Two weeks prior to initiation of the carcinogen treatment, the animals were placed on a semisynthetic diet to which either no selenium or 1 or 5 mg selenium/kg of diet as sodium selenite was added. There were 31 to 34 animals per group. Animals were maintained on their respective diets for the duration of the study, which was terminated 195 days after the first MNU treatment. No significant differences among groups were observed in the incidence of either benign lesions or carcinomas. The distribution of tumor type was similar, irrespective of selenium treatment. Therefore, selenium exerted no protective effect against MNU-induced tracheal carcinogenesis.

f. Virus - induced Neoplasia

In another study (Exon et al. 1976) rats were either selenium supplemented or deficient and subsequently challenged with an oncogenic virus (Ranscher leukemia virus). The incidence of neoplasia was similar for all treated groups compared to the control virus-inoculated animals. Thus, selenium neither protected nor enhanced virus-induced neoplasia.

H. Summary

Selenium appears to be a necessary micronutrient for most laboratory animals, livestock and poultry. Selenium deficiency has been associated with necrosis of the liver, kidneys, skeletal muscle, pancreas and heart of laboratory animals; muscular dystrophy and myopathy of livestock; and pancreatic degeneration of chickens. Dietary levels necessary to prevent these effects in livestock and laboratory animals have been reported to range from 0.10 mg Se/kg of feed for cattle, sheep, swine, rats and mice to 0.15 mg Se/kg of feed for poultry.

The acute toxicological dose of selenium in livestock and laboratory animals varies greatly with the species studied, method of administration, form of selenium, and criteria of toxicity. The minimum oral lethal dose for cattle is reported to be 3 mg Se/kg-bw; a subcutaneous 100% lethal dose for swine is 2 mg Se/kg-bw in 3 hours and 1.2 mg Se/kg-bw in five hours. The organic selenium compounds are much less toxic for rats than are selenites (3.25 mg Se/kg-bw) which are more toxic than selenates (5.25 mg Se/kg-bw).

The chronic toxicity of selenium has been studied in laboratory animals and livestock. Chickens fed 8 mg/kg of Se in their feed showed reduced egg production, weight and egg hatchability. A dose of 0.5 mg Se/kg in feed (sodium selenite) resulted in hyperplastic liver lesions in rats and concentrations of 0.25 mg/kg resulted in liver lesions; whereas decreased growth rate (4 mg/kg), and death after 90 days (6 to 16 mg/kg) were observed at higher doses.

Selenium interacts with other compounds and affects toxicity. Fluoride has been shown to increase the toxicity of selenium in rats and selenium has been suggested to reduce the toxic effects of silver, thallium paraquat, sulfate, arsenic, cadmium and mercury.

Selenium is teratogenic in chickens at doses of 8 to 10 mg/kg selenite in the feed and as low as 0.01 mg/kg of egg contents. It is teratogenic to frog (Xenopus laevius) embryos at levels between 1 mg/L and 2 mg/L in the water. There is no experimental evidence of selenium's teratogenicity in mammals; however, there are reports of teratologic change in mammals pastured on seleniferous ranges. Selenite will cause lower birthweights and poor survivability in offspring at levels sufficient to cause selenosis in the mother. The teratogenic effect of organoselenium compounds has not been studied.

Sodium selenite has been reported to enhance the mutagenicity of N-OH-AAF in Salmonella tester strain TA 1538. However, Jacobs (1977) showed an inhibition of N-OH-AAF mutagenesis in the same strain using sodium selenite. Neither sodium selenite nor sodium selenate has been reported mutagenic in Salmonella strains TA 98 or TA 1537. However, both salts were mutagenic in strain TA 100.

It has been concluded that sufficient studies have not been completed to establish selenium as a carcinogen (IARC 1975, NAS 1976); whereas there are numerous reports that selenium compounds have anticarcinogenic properties. Studies in rats have demonstrated that both sodium selenide and sodium selenite reduced the incidence of tumors following administration of various carcinogens with different target sites, i.e., skin, liver, lung, colon or mammary glands. Thus, selenium as selenite and selenate appears to possess certain anticarcinogenic properties.

VI. HEALTH EFFECTS IN HUMANS

A. Human Nutritional Requirements

Selenium should be listed among the trace elements which are essential for human nutrition (Thomson and Robinson 1980). While selenium deficiency has clearly been associated with health problems in animals (see Section V), data on human requirements are not as readily available. However, total parenteral feeding experience in humans indicates that hyposelenium states exist (Thomson and Robinson 1980, Van Rij et al. 1979); moreover, at least one form of cardiac disease, Keshan disease, appears to be related to selenium deficiency.

Keshan disease, characterized by heart failure, cardiac enlargement, abnormalities of EKG, gallop rhythm and even cardiogenic shock, occurs predominately in children and women of child-bearing age in the People's Republic of China (Keshan Disease Research Group 1979a,b). Supplementation of the diet with sodium selenite (0.5 mg weekly, 1 to 5 years old; 1.0 mg weekly, 6 to 10 years old) appears to prevent or reverse the disease. Additional evidence that selenium is involved in the pathophysiology of the cardiovascular system is suggested by the observation that the death rate due to cardiovascular disease has been alleged to decrease in areas where the selenium content of the soil is high (Shamberger et al., 1975).

The relationship between selenium and the antioxidant vitamin E was elucidated by Rotruck et al. (1973). They demonstrated that selenium is a component of the peroxide-metabolizing enzyme, glutathione peroxidase. Thus vitamin E and selenium act to provide a natural defense against peroxidative damage (Hoekstra 1975). Human erythrocyte glutathione peroxidase contains selenium (Awasthi et al. 1975). Children with kwashiorkor have been shown to have low blood concentrations of selenium (B rk 1976) and to respond with reticulocytosis to selenium administration (Hopkins and Majaj 1967).

Total parenteral nutrition in the absence of selenium supplementation has been reported in one patient to result in muscle discomfort, particularly of the quadriceps and hamstrings within 30 days (Van Rij et al. 1979). The plasma selenium concentration of the patient was 9 ng/mL (0.009 μg/mL). In addition to pain on motion, the muscles were tender and there was limitation of motion. Supplementation of the parenteral nutrition with 100 μg selenium per day for one week relieved the symptoms but did not raise plasma selenium or red cell $GSHP_x$ concentrations significantly.

Chronic selenium deficiency has also been alleged to cause muscle weakness and stiffness in people in selenium-deficient areas of New Zealand (Thomson and Robinson 1980), but the results appear to be somewhat subjective. There is some evidence of muscle weakness and discomfort in postsurgical or cancer patients on parenteral nutrition in selenium-deficient areas, but since other factors could be involved confirmation is required (McKenzie et al. 1976, Jacobsson and Wester 1977). Human fibroblasts in culture require selenium supplementation for growth (McKeehan et al. 1976).

A number of diseases have been associated with decrease in $GSHP_x$ activity. Among these are neuronal ceroid lipofuscinosis (Westermarck and Sandholm 1977) and multiple sclerosis (Shukla et al. 1977). Whether these or other conditions are caused by $GSHP_x$ deficiency as a result of selenium deficiency has not been established, but $GSHP_x$ concentration in erythrocytes has been shown to diminish in cases of selenium deficiency (Rea et al. 1979, Thomson et al. 1977).

As presented in greater detail in Section III, Toxicokinetics, a very small percentage of ingested selenium is stored in the body with the primary excretion routes being the urine and feces (Thompson 1972). This imples that selenium must be ingested daily to maintain the blood and tissue concentrations deemed necessary for adequate human nutrition (Stewart et al. 1978). Since selenium ingestion varies greatly worldwide, depending on the local soil and plant content, this is of particular importance for those areas that are selenium deficient.

Selenium concentrations in the blood are significantly lower in infants than in adults (Rudolph and Wong 1978, Rhead et al. 1972). Selenium deficiency and low concentrations of $GSHP_x$ activity, with its relationship to vitamin E, have been implicated in the sensitivity of newborn and premature infants' erythrocytes to oxidant stress (Ganther et al. 1976). This may be increased in infants fed cow's milk formulas which contain less selenium than human breast milk (Gross 1976, Millar and Sheppard 1972). The possibility that selenium deficiency coupled with vitamin E inadequacy might underlie the sudden infant death syndrome has been suggested (Money 1970), although this has been questioned in other studies (Rhead et al. 1972, 1973).

It would appear from this brief summary that selenium plays an important role in maintenance of normal human health throughout life, and while the intake and content can vary over a wide range, selenium ingestion may be required on a daily basis. Based on animal requirements, an intake of about 0.1 μg of selenium per gram of diet would appear to be an adequate maintenance level for adult humans (Levander 1976). Human studies indicate that a total intake of 60 to 120 μg of selenium per day seems to be adequate to prevent deficiency (Levander 1976).

A safe and adequate selenium intake has been recently established by the Food and Nutrition Board of the National Research Council (NAS 1980b) which has recommended 50 to 200 μg Se/day in adults and lower amounts in infants and children (Table VI-1). The average adult intake in this country has been estimated at 130 to 150 μg/day in some studies which means that selenium intake is, generally, quite adequate (Watkinson 1974, Schroeder et al. 1970).

B. Acute Toxicity

Acute accidental exposure to selenium fumes during the melting of scrap metal has resulted in localized toxic symptoms within two minutes (Wilber 1980). Symptoms reported were immediate intense irritation of the nose, throat and eyes and an intense sour garlic odor on the breath. Burning of the

Table VI-1. Safe and Adequate Ranges of Daily Selenium Intake.[a]

Group	Age (years)	Daily selenium intake (μg)
Infants	0.0-0.5	10-40
	0.5-1	20-60
Children	1-3	20-80
	4-6	30-120
	7+	50-200
Adults		50-200

[a] Adapted from USEPA (1980) and NAS (1980)

nasal mucosa was noted and severe headaches developing immediately and lasting about 24 hours were reported. Irritation of the mucous membranes has been reported to persist for months following exposure. These are apparently long-lasting effects of acute exposure, rather than toxic symptoms.

Hydrogen selenide is a toxic gas which may cause fatalities. Symptoms of acute exposure include nausea, vomiting, metallic taste in the mouth, garlic odor of the breath, dizziness and lassitude (Wilber 1980).

A single case of acute selenium intoxication resulting in a fatality has been reported (Carter 1966). A child who drank gun-blueing compound containing 1.8% selenious acid had clinical signs of acute toxicity including peripheral vascular collapse, pulmonary edema and coma. Autopsy revealed pulmonary congestion, hemorrhage and edema. Necrosis in liver and kidneys was not described. The tissue concentrations of selenium were not reported.

The NIOSH Draft Technical Standard and Supporting Documentation for Selenium Compounds (NIOSH 1980) states that elemental selenium and some selenium compounds including vapors, dusts and fumes are irritating to the eyes, upper respiratory tract and skin. They report on workers exposed to an "undetermined" concentration of selenium oxide that resulted in bronchospasm and dyspnea followed within 12 hours by fever and chills, headache, bronchitis and a few cases of pneumonitis. All workers became asymptomatic within a week. In workers exposed to selenium in a selenium plant at measured levels of 0.2 to 3.6 mg/m^3, urinary levels ranged from below 0.1 to as high as

0.43 mg Se/L of urine. The workers reported metallic taste, garlic odor of breath and gastrointestinal disturbances.

The NIOSH (1980) also cited several cases describing the ocular effects of exposures to various selenium compounds. Direct spray of selenium dioxide in unknown concentration into the eyes of a chemist produced burns and irritation with corneal dulling within 16 hours. In 16 days vision and cornea were entirely normal. Acute burns and vesication can be produced by selenium oxide and selenium oxychloride. NIOSH (1980) also quoted a statement by the International Labor Organization (1972) that "the elemental forms of selenium are probably completely harmless to man..." and concluded that no available literature demonstrated that elemental selenium was harmful to the eye.

It appears then that selenium compounds, but not selenium per se, produce acute effects by direct toxic action. Acute toxic effects due to selenium uptake and metabolism or induction of hypersensitivity has not been adequately investigated in humans. Measurement of acute toxic concentrations in humans are largely lacking, and for the most part human toxic doses are projected from animal experimentation.

C. Chronic Toxicity

Although industrial exposure can lead to toxic responses due to accumulation of excessive amounts of selenium in tissues and blood, the recorded symptoms have been more frequent in seleniferous areas. The symptoms and signs of acute and chronic toxicity are summarized in Table VI-2. Bioaccumulation of selenium is known to occur in human as well as animal tissues. Concentrations of 0.2 ppm (0.2 mg/L) in human whole blood have been recorded (Shapiro 1973) (see Tables VI-3, VI-4).

The earliest and most characteristic manifestations of excess selenium absorption by the body is garlic odor of the breath (Wilber 1980). This may be preceded by a subtle "metallic" taste in the mouth. When workers are removed from selenium exposure, the signs will usually disappear within seven to ten days. The remaining signs of selenium absorption are general and non-specific. Thus, there remains some question of whether all symptoms are related to excessive selenium accumulation. The symptoms include: pallor, lassitude, irritability, vague symptoms of indigestion and giddiness (Wilber 1980, Shapiro 1973). While liver and kidney damage have been documented in animals, evidence in humans is scanty and requires further study.

Smith et al. (1937) studied dietary intake and excretion of farmers in seleniferous areas and presented suggestive evidence that chronic selenium ingestion may result in general lassitude, pallor, fatigue and vertigo as well as other non-specific systemic symptoms. They also reported dyspepsia, nail changes, jaundice, chloasma, arthritis and edema. Smith et al. (1937) reported that "it is not certain that any one (symptom) is the direct result of continual ingestion of selenium." It is difficult to evaluate these

Table VI-2. Symptoms and Signs of Selenium Toxicity.[a]

		Symptoms/Signs		
Route of Exposure	Organ or Site	Acute	Chronic	Compounds
Aerosol (fumes)	Eyes	Pain, burning	NS[b]	SeO_2
	Skin	Burns	NS	SeO_2
		Allergy:		
		Urticaria	NS	SeO_2
		Rose eye	NS	SeO_2
	Stomach	Dyspepsia	NS	SeO_2
	Mucous membranes	Irritation, cough	NS	H_2Se
	Lungs	Pulmonary edema, potentially lethal	NS	H_2Se
Contact	Skin	Vesication, burns	NS	$SeOCl_2$, Se_2Cl_2
Ingestion	General	NS	Pallor; fatigue	NS
		NS	Lassitude; vertigo	NS
	Skin	NS	Itching	NS
		NS	Dermatitis	NS
	Gastro-intestinal	NS	Dyspepsia	NS
	Other	NS	Hair loss;	NS
			caries	NS
		NS	Garlic breath	NS
		NS	Discoloration of nails	NS

---

[a] From Glover (1970) and Shapiro (1973)

[b] NS = Not specified

Table VI-3. Selenium Content in Human Tissues (Necropsy Data) (µg Se/g Whole Tissue).[a]

	Sex:	M	ND[b]	F	M	M	ND	M	M
	Age:	9 months	"Infant"	15 years	41 years	68 years	"Adult"	29 years	64 years
Type of Tissue	Location:	Vermont	Canada	U.S.S.R	Vermont	Vermont	Canada	U.S.S.R	U.S.S.R
Liver		0.33	0.34	0.79	0.42	0.81	0.39	0.58	1.61
Lung		0.24	0.17	0.24	0.26	0.20	0.21	1.38	1.00
Heart		0.25	0.55	0.04	0.25	0.26	0.22	0.72	1.14
Kidney		0.70	0.92	0.80	0.75	1.84	0.63	2.71	1.61
Spleen		0.47	ND	0.18	0.29	0.32	ND	0.76	0.78
Bone (rib)		0.42	ND	0.21	ND	ND	ND	0.34	0.243
Muscle		0.18	ND	0.16	0.17	0.36	ND	0.28	2.26
Pancreas		0.34	0.37	0.32	0.29	0.27	0.27	0.26	1.00
Testes		0.15	ND	NA[c]	0.36	0.38	ND	ND	ND
Brain		0.04	0.16	ND	0.21	ND	0.27	ND	ND
Small intestine		0.18	ND	ND	0.32	0.12	ND	ND	ND
Fat		ND	ND	ND	0.04	ND	ND	ND	ND
Skin		ND	ND	0.12	ND	ND	ND	0.28	1.24
Gonad		ND	0.46	ND	ND	ND	0.47	ND	ND
Thyroid		ND	0.64	ND	ND	ND	1.24	ND	ND

[a] From Shapiro (1973)
[b] ND = No data
[c] NA = Not applicable

Table VI-4. Selenium Concentrations in Whole Blood from 19 Collection Sites in the United States.[a,b]

Collection Site	No. of Samples	Mean[c] (μg/100 mL)	Standard Error (μg/100 mL)	Range (μg/100 mL)
Rapid City, S.D.	20	25.6	3.6	20-34
Cheyenne, Wyo.	10	23.4	2.5	20-27
Spokane, Wash.	10	23.0	3.3	18-28
Fargo, N.D.	10	21.7	3.6	18-30
Little Rock, Ark.	10	20.1	2.8	15-24
Phoenix, Ariz.	10	19.7	3.4	15-25
Meridian, Miss.	10	19.5	4.4	14-27
Missoula, Mont.	20	19.4	3.1	12-25
El Paso, Tex.	10	19.2	3.4	15-26
Jacksonville, Fla.	10	18.8	3.0	15-26
Red Bluff, Calif.	10	18.2	4.5	12-27
Geneva, N.Y.	10	18.2	2.2	15-22
Billings, Mont.	10	18.0	4.9	10-27
Montpelier, Vt.	10	18.0	1.6	16-20
Lubbock, Tex.	10	17.8	2.9	12-24
Lafayette, La.	10	17.6	2.4	14-22
Canandaigua, N.Y.	10	17.6	2.0	14-20
Muncie, Ind.	10	15.8	2.4	11-20
Lima, Ohio	10	15.7	3.2	10-20
Summary	210	20.6		10-34

[a] Shapiro (1973)

[b] The specimens used in this study were obtained from blood banks making collections in different cities and towns in the United States.

[c] The mean for Rapid City, S.D., is significantly ($P<0.05$) greater than the mean for all other cities, except Cheyenne, Spokane, and Fargo. The mean for Fargo, N.D., is significantly ($P<0.05$) greater than the means for Muncie, Ind., and Lima, Ohio, but not significantly different from the means for the other 16 location sites.

symptoms in view of the lack of adequate controls. However, the range of continuous daily intake of selenium was probably 0.01 to 0.1 mg/kg-bw and possibly as much as 0.2 mg/kg-bw.

In Shapiro's analysis (1973) there was some correlation between symptoms of selenosis and urinary content greater than 0.2 μg Se/mL. He concluded that the evidence favored the existence of chronic selenium toxicity of dietary origin in humans. A controlled study with blood, urine and even tissue levels in humans will be required before such a conclusion can be firmly established.

Yang et al. (1983) examined endemic selenium intoxication in humans in China. The study documented at least four levels of selenium consumption in humans: high selenium with chronic selenosis, high selenium in the absence of selenosis, selenium adequate and low selenium manifest by Keshan disease. The daily dietary intake of selenium averaged 4.99 mg/day for the group with chronic selenosis. For the group in the high selenium area without selenosis, a mean daily intake of 0.75 mg was reported, with a maximum level of 1.51 mg/day.

D. Teratogenicity

Little definitive research exists implicating selenium as a teratologic or embryotoxic agent in humans. As with the early work on animals in seleniferous environments, there are anecdotal reports of human monstrosities. Rosenfeld and Beath (1964) reviewed a paper by Benavides and Mojica (1959) who recount descriptions by a priest in Colombia in 1560. They state:

> "the corn as well as other vegetables grow well and healthy, but in some regions it is so poisonous that whoever eats it, man or animal, loses his hair. Indian women gave birth to monstrous-looking babies who were abandoned by their parents. Some abnormal looking babies born to Indian mothers were described to be covered with coarse brittle hair. A number of travelers and priests have repeatedly commented on abandoned malformed babies."

Reports in 1856 of aborted animals and eggs that failed to hatch and abnormalities of chicks similar to those described for selenium in the United States have also been described in the same areas of Colombia where the human problems were reported. In addition, as late as 1936 human cases of chronic selenosis in these areas were reported (Rosenfeld and Beath 1964).

Hadjimarkos et al. (1959) reported that in seleniferous areas of the United States dental caries correlated with the high selenium intake in humans. They also analyzed placental and umbilical cord blood for selenium of humans that resided in a nonseleniferous area and reported a 1.5:1 ratio and contrasted this with 3:1 or 6:1 for fluorides. Their conclusion is that selenium is transplacentally transported more efficiently than fluoride.

Robertson (1970) reported a high incidence of abortion in five pregnancies occurring in technicians who had the potential of being exposed to airborne sodium selenite powder. Four of these five women aborted; however, two of the abortions could be linked to clinical factors other than selenium exposure.

Shamberger (1971), acting on Robertson's hypothesis, surveyed neonatal death rates in high-, medium- and low-selenium states of the United States and found an inverse relationship between selenium and neonatal death.

Hadjimarkos (1970) has pointed out that his work on dental caries would indicate that individuals in seleniferous areas consumed up to ten times the selenium in the diet of normal controls.

Clegg (1971), in commenting on Robertson's and Hadjimarkos' findings, concludes that while high concentrations of selenium in the diets of city dwellers is unlikely, the rural populations in seleniferous areas may be at risk.

In light of the suspected transport of selenium compounds across the human placenta and the unknown extent to which chronic selenium dosing to pregnant women can be sequestered, it seems prudent to be concerned about potential human fetal risk. The accounts of human teratology related to seleniferous soils should not be dismissed lightly. The parallel exists between these accounts and the accounts of animals on seleniferous ranges. Organoselenium compounds may cross the placenta more easily than selenite and may be more sequestered in the fetus. Based on animal teratological data, it is unlikely that a single large exposure of selenium will cause teratologic consequences. Yet the effects of chronic exposure to selenium from dietary or other sources may produce effects previously not documented by controlled animal experiments in which selenium compounds have been artificially added. No quantitative data exist for human exposures relative to teratology.

E. Mutagenicity

Paton and Allison (1972) have reported the effects of sodium selenate and sodium selenite on chromosomal aberrations (breaks and exchanges) in cultures of human leukocytes. At least two subtoxic doses (concentrations not specified) of Na_2SeO_3 and Na_2SeO_4 were tested with 24, 48 and 72 hours of exposure. No chromosomal aberrations were observed for either selenium salt. Other salts, similarly tested, produced chromosomal aberrations in varying degrees.

Nakamuro et al. (1976) studied the effects of five selenium compounds (Na_2SeO_3, H_2SeO_3, Na_2SeO_4, H_2SeO_4 and SeO_2) on the induction of chromosomal aberrations in cultured human leukocytes, on DNA-modifying activity (*Bacillus subtilis rec*$^{+-}$assay) and on inactivation of transforming activity in *Bacillus*. Leukocytes were exposed to 13 to 53 x 10^{-5} M Na_2SeO_3, H_2SeO_4 or Na_2SeO_4 or 6.5 to 26 x 10^{-5} M H_2SeO_3 or SeO_2 for 24 hours. Control cultures, exposed to water (the vehicle) only, had 7.6 chromosomal aberrations per 100 cells, all of which constituted gaps. Chromosomal aberrations were significantly higher for compounds with 4-valent than 6-valent selenium, the efficiencies being in the decreasing order $H_2SeO_3 > Na_2SeO_3 > SeO_2 > H_2SeO_4 > Na_2SeO_4$. Except for Na_2SeO_4, dose-dependent effects were observed for all compounds, with the highest number of aberrations observed (182/100 cells) with 26 x 10^{-5} M H_2SeO_3. In all cases most of the aberrations represented chromatid gaps with much lower frequencies of chromosomal breaks and chromosomal exchanges. In the *Bacillus subtilis rec*$^{+-}$ assay, the selenites (Na_2SeO_3 and H_2SeO_4) but not the selenates (Na_2SeO_4

and H_2SeO_4) produced damage to DNA. Dose responses were seen at 0.8 to 10 mg Se/plate with a pH of 7.2 in the culture medium and a pH of 8.0 to 7.0 of an Na_2SeO_3: H_2SeO_3 (4:1) aqueous solution. A significant loss of transforming activity (tryptophan marker) in Bacillus subtilis was not observed for Na_2SeO_4, H_2SeO_4 or Na_2SeO_3, but treatment with H_2SeO_3 and SeO_2 at 1.6×10^{-3} M yielded approximately 30% loss of transforming activity as compared with untreated DNA.

Lo et al. (1978) found that at doses varying from 8×10^{-5} to 3×10^{-3} M and relatively short exposure times (0.5 to 1.5 hours), Na_2SeO_3 induced DNA fragmentation, DNA repair synthesis, chromosomal aberrations, and a mitotic inhibition in cultured human fibroblasts. The response of DNA repair-deficient Xeroderma pigmentosum (XP) fibroblasts to Na_2SeO_3 was comparable to that of the normal human fibroblasts. Incubation with mouse liver 9000xg supernatant fraction increased the capacity of Na_2SeO_3 to induce chromosome aberrations, DNA repair synthesis and a lethal effect. XP cells responded likewise when treated with similarly activated selenite. Na_2SeO_4 at 7×10^{-6} to 2×10^{-3} M produced effects on DNA repair, mitotic rate and clone-forming capacity (toxicity) similar to those of Na_2SeO_3 tested at equimolar concentrations. However, unlike Na_2SeO_3, Na_2SeO_4 at doses ranging from 8×10^{-5} to 3×10^{-3} M could not be activated by incubating with mouse liver 9000xg supernatant preparation. An exception here was a small but significant increase in DNA repair synthesis at 10^{-2} M when the activation mixture was present.

Ray et al. (1978) tested Na_2SeO_3 for its sister-chromatid exchange (SCE)-inducing ability in human whole blood cultures and for the effect of its co-exposure with methyl methanesulfonate (MMS) or N-hydroxy-2-acetylamino-fluorene (N-OH-AAF) on SCE-frequency. Long exposure times (77 and 96 hours) to 3.95×10^{-6} M Na_2SeO_3 resulted in cell death as measured by mitotic indices, but mitotic figures were present after exposure to higher concentrations for a shorter time (19 hours). High Na_2SeO_3 concentrations (7.9×10^{-6} and 1.19×10^{-5} M) resulted in a threefold increase in SCE frequency above the background frequency (6 to 7 SCEs/cell). Exposure of lymphocytes at 1×10^{-4} M MMS for the last 19 hours of culture yielded an average SCE frequency of 30.17 ± 0.75, whereas a similar exposure to 2.7×10^{-5} M N-OH-AAF resulted in 13.61 ± 0.43 SCEs/cell. Simultaneous addition of the high Na_2SeO_3 concentrations and MMS or N-OH-AAF to the cultures resulted in SCE frequencies that were 25% to 30% and 11% to 17%, respectively, below the sum of the SCE frequencies produced by the individual compounds. It was concluded that, although Na_2SeO_3 induces SCE in human whole blood cultures, it also decreases the SCE-inducing abilities of MMS and N-OH-AAF in this system.

Ray and Altenburg (1978) studied the induction of sister-chromatid exchanges by Na_2SeO_3 in both short-term and long-term human cell cultures tests. The ability of Na_2SeO_3 to induce SCEs was found to depend on the culture condition employed. Concentrations of Na_2SeO_3 (7.9×10^{-6} M and greater) that produced elevated SCE frequencies in whole blood cultures resulted in control level SCE frequencies (6 to 8 SCEs/cell) in Ficoll-Hypaque-purified lymphocyte cultures. However, whole blood and purified lymphocyte cultures were equally sensitive to SCE induction by methyl methanesulfonate, ethyl methanesulfonate and N- hydroxy-2-acetylaminofluorene. Analysis of different whole blood components showed that the presence of red blood cells (RBCs), specifically RBC lysate, was a prerequisite for Na_2SeO_3 SCE induction in purified lymphocyte cultures. The SCE frequencies of Xeroderma pigmentosum (XP12RO) and normal human lymphoblastoid cell lines were also found to be unaffected by Na_2SeO_3 concentrations that produced elevated SCE frequencies in whole blood cultures. Incubation of these latter two cell types with Na_2SeO_3 and RBC lysate resulted in SCE frequencies comparable to those in Na_2SeO_3-exposed whole blood culture. It was concluded that exposure of Na_2SeO_3 to RBCs and RBC lysate possibly results in a chemical modification of Na_2SeO_3 which enables it to induce SCEs.

Ray and Altenburg (1980) also tested inorganic selenium compounds, having selenium in different valence states, for their ability to induce SCEs in human whole blood cultures. The selenium compounds tested (and their valence states) were: sodium selenide (Se^{2-}), selenium dioxide (Se^{4+}), selenium (Se^0), sodium selenite (Se^{4+}) and sodium selenate (Se^{6+}). Human whole blood cultures were exposed to concentrations of these compounds ranging from 1.12×10^{-6} to 8.00×10^{-5} M for the final 18 hours of a 96-hour incubation period. Except for sodium selenate, all compounds induced SCEs at the highest concentration tested (1.6 to 4.8×10^{-5} M). Selenium (Se^0) was the most potent inducer of SCEs (29.76/cell at 1.6×10^{-5} M) and sodium selenite was the least effective (17.45/cell at 3.95×10^{-5} M), while selenium dioxide and sodium selenide had intermediate SCE-inducing activities (22.20 and 23.68/cell, respectively, at 4×10^{-5} M).

Ray and Altenburg (1980) pointed out that their results agree with those of Lo et al. (1978) and Nakamuro et al. (1976) in that selenites had much higher SCE-inducing activity than selenates. However, in contrast to the results of Nakamuro et al. (1976), Ray and Altenburg (1980) found that selenium dioxide (SeO_2)-treatment resulted in slightly greater increases in SCE frequency than did sodium selenite (Na_2SeO_3). In the study of Nakamuro et al. (1976), Na_2SeO_3 induced higher frequencies of chromosomal aberrations in cultured human leukocytes than SeO_2. Ray and Atenburg (1980) pointed out that the differences were small and could probably be neglected because SeO_2 in aqueous solution would be expected to form selenious acid (H_2SeO_3) which theoretically may be metabolized similarily to Na_2SeO_3.

Whiting et al. (1980) examined the effects of inorganic and organic selenium compounds on unscheduled DNA synthesis (UDS) in cultured human diploid fibroblasts. Glutathione strongly enhanced the induction of UDS by inorganic selenium compounds: Na_2SeO_4, Na_2SeO_3 and Na_2Se. In the presence of 10^{-3} M glutathione, high levels of UDS (74 to 114 grains per nucleus) were observed in cells treated with Na_2SeO_4 (10^{-3} M), Na_2SeO_3 (10^{-5} to 3×10^{-4} M) and Na_2Se (10^{-5} to 10^{-3} M). Glutathione at 10^{-4} or 10^{-2} M caused less enhancement of UDS. In the absence of glutathione, these inorganic selenium compounds induced low levels of UDS (up to 13 grains per nucleus). Three organic compounds (selenocystine, selenocystamine and selenomethionine) were also examined for UDS induction. No UDS was detected in cells treated with selenocystamine or selenomethionine, with or without added glutathione. However, selenocystine alone at 10^{-4} to 10^{-3} M induced a low level of UDS;

glutathione enhanced UDS, with a maximum effect (22 grains/nucleus) at 10^{-2} M glutathione. This effect was about 20% of that detected in cells treated with inorganic selenium compounds in the presence of one-tenth that concentration (10^{-3} M) of glutathione. Since glutathione is a reducing agent; it was concluded that a reduction is involved in the conversion of selenium compounds to mutagenic forms. It was speculated that the active mutagenic forms may be selenols, reduced glutathione-selenium (GS-Se-) species derived from inorganic selenium, and reduced selenium (R-Se-) species derived from organic selenium compounds.

No direct assessments of mutagenesis of selenium compounds in humans were located in the available literature. Therefore it is virtually impossible to extrapolate the concentrations from *in vitro* studies to *in vivo* concentrations which might be mutagenic.

F. Carcinogenicity

There is no evidence that naturally ocurring selenium compounds are carcinogenic in humans. On the contrary, epidemiological studies suggest that selenium may be protective against human cancer. Shamberger and Frost (1969) were among the first to report that an inverse relationship existed between cancer death rates and the selenium concentrations in foliage plants of several Canadian provinces. The human cancer death rate in provinces with selenium-containing plants was 122.2 ± 7.8 (presumably per 100,000 population although this was not specified), while in the provinces devoid of these plants, the human death rate was 139.9 ± 4.0. Further epidemiological studies correlated an increased incidence of colon, breast and other forms of cancer in humans in geographic areas where selenium is deficient and a lowered cancer incidence with higher selenium concentrations (Shamberger and Willis 1971, Schrauzer and Ishmael 1974, Shamberger 1976, Schrauzer et al. 1976, Jansson et al. 1978).

Attempts have also been made to correlate blood and tissue selenium concentrations with the presence of cancer in humans. On the average, the blood of cancer patients was reported to contain less selenium than the blood of non- cancerous patients (Schrauzer and Rhead 1971, Shamberger et al. 1973, Broghamer et al. 1976, 1978, McConnell et al. 1980). However, the blood of patients with some forms of cancer (Shamberger and Willis 1971) contained concentrations of selenium within the normal range of 10 to 34 µg Se/100 mL (0.1 to 0.34 mg Se/L) reported by Allaway et al. (1968).

Griffin (1979), in a review article, stated the following:

> "Whether selenium levels in the body, diet and environment are major factors in terms of human cancer is indeed a complex issue and in the writer's opinion a largely unresolved one. Selenium, as already indicated, is highly ubiquitous in distribution and is present in many chemical forms. These factors along with the long latency period in terms of carcinogenesis and the present trend of individuals in locale, occupation, and travel, as well as medical records, diagnosis and autopsy reports, etc., make it indeed difficult for precise correlations between selenium and cancer causation and/or prevention."

A similar conclusion was made in a report by the International Agency for Research on Cancer (IARC 1975). The report stated:

> "The available data provide no suggestion that selenium is carcinogenic in man, and the evidence for a negative correlation between regional cancer deaths and selenium is not convincing."

G. Epidemiology Studies

The epidemiologic investigations of the effects of selenium on human health have been concerned mainly with three areas of study: (1) the effects on the cardiovascular system; (2) the relationship to cancer; and (3) the exposure of workers in industrial plants which make use of selenium in part of their manufacturing process and the exposure of community populations that exist in areas where there is a known high content of selenium in the surrounding soil and water. In addition to these major areas, there has been some speculation concerning the role that selenium may play in certain neurologic diseases, teratogenesis and dental caries.

1. Cardiovascular

Recently, reports from mainland China describe a cardiomyopathy of humans called Keshan disease (Johnson et al. 1981). The incidence of this disease is high in communities where there is a known selenium deficiency in the soil. Studies from China have demonstrated in controlled therapeutic trials that the prophylactic administration of sodium selenite prevented new cases of Keshan disease.

Westermarck et al. (1977), in a study of the selenium content of whole blood in the serum in adults and children of different ages from different parts of Finland, report that there is an inverse relationship between hypertension and the serum concentration of selenium in human populations. The blood pressure of adult Lapps and Skolts in northern Lapland has been reported as being lower than that of other Finns (Sundberg et al. 1975), and the highest selenium serum levels in the Finnish population was found among Lapps from the same area.

Westermarck et al. (1977) noted that in the low-selenium areas, namely the eastern part of Finland, the death rate among the male population from degenerative heart disease is the highest in the world. Shamberger et al. (1975) reported similar findings when studying cadiovascular mortality rates in relation to selenium content (of forage crops) of geographic areas in the United States. The age-specific death rate for cardiovascular, cerebral vascular, coronary and hypertensive heart disease were all significantly ($P<0.001$) lower in the very high-selenium areas than in the low-selenium areas of the United States.

2. Relationship to Cancer

In recent years, cancer researchers have been interested in antioxidants as possible anticarcinogens. Antioxidants include certain carotenes, vitamin A, vitamin E, disulfiram and selenium. Dietary administration of selenium has shown its powerful anticarcinogenic properties in animal experimentation (Shamberger 1970). It is believed that an antioxidant may work by inhibiting the transformation of a pre-cancer lesion that needs oxidation for its metabolic transformation. Epidemiologic studies in the United States support this activity of selenium.

Shamberger and Willis (1971) demonstrated a striking correlation between decreased cancer death rates in humans and an increase in the selenium in the forage crops in California. In high-selenium areas (selenium 0.11 ppm of forage crops) the cancer death rate per 100,000 was 141.2. In the medium-selenium areas (0.05 to 0.10 ppm) the cancer death rate was 190.1. In low selenium areas (0.02 to 0.05 ppm) the death rate was a striking 233.0.

Shamberger and Willis (1971) also demonstrated a similar relationship between increased cancer mortality rates and decreased concentrations of selenium in forage crops of various areas in the United States. Cancer mortality rates for states classified as high-, medium- or low-selenium areas (according to the content in forage crops) were compared. High-selenium areas included Alabama, Arizona, Arkansas, Colorado, Iowa, Kansas, Louisiana, Mississipi, Missouri, Montana, Nebraska, Nevada, New Mexico, North Dakota, Oklahoma, South Dakota, Texas, Utah and Wyoming. Medium-selenium areas included California, Georgia, Idaho, Kentucky, Minnesota, North Carolina, Oregon, South Carolina, Texas, Virginia and Washington. Low-selenium areas included Connecticut, Delaware, Florida, Illinois, Indiana, Maine, Maryland, Massachusetts, Michigan, Ohio, Pennsylvania, Rhode Island, Vermont, West Virginia and Wisconsin. The median values for cancer mortality rates were 126.0 and 127.0/100,000 for the high- and medium-selenium states and 175.0 for the low-selenium states. Shamberger also noted that the death rate for individual types of cancer for both males and females markedly decreased in the high-selenium areas. These included lymphomas, and cancer of the digestive organs and peritoneum, lungs and breasts.

Similar correlations have been noted worldwide (Jansson et al. 1978). Selenium-deficient regions such as Denmark, Sweden, New Zealand and Australia have high colon, rectal and breast cancer rates; selenium-adequate areas such as Japan have low rates for these cancers.

In addition, McConnell et al. (1975) and Broghamer et al. (1976) have both reported significantly lower mean serum selenium concentrations in patients with gastrointestinal cancer compared to patients with other disorders.

Willett et al. (1983) reported a similar relationship between cancer and low serum selenium concentrations in a retrospective study of hypertensive subjects who developed cancer between 1973 and 1975. The 111 subjects who developed cancer and 210 cancer-free controls (matched for age, sex, race, smoking history, reported usage of hypertensive medications, initial blood pressure and month of initial blood sample collection) were selected from a large community-based hypertension study. In 1973, serum samples from the participants (10,940 men and women, ages 30 to 69) of the community-based study were obtained, frozen and stored. Serum samples from subjects that developed cancer and selected controls were subsequently retrieved and selenium was determined by neutron activation analyses. The mean serum selenium concentrations of the cancer cases was significantly lower than that of controls (P = 0.02) with the strongest association for gastrointestinal and prostatic cancers. Although all subjects were hypertensive, the authors concluded that the subjects were reasonably representative of the U.S. population and that the results support the inverse relationship between selenium intake and cancer incidence.

3. Industrial and Community Studies

Valentine et al. (1978) studied the correlation of selenium in the blood, hair, urine and tap water from a study population consisting of 43 residents from a small community in Milan, New Mexico, exposed to varying amounts of selenium via water from home wells. They found that the correlation between selenium concentrations in blood and the concentration in well-water was not statistically significant ($P>0.05$). Urinary selenium concentrations were significantly correlated to hair ($P<0.001$) and blood ($P<0.05$) concentrations. The correlation between hair and blood concentrations was not significant ($P>0.05$). Hence in studies for chronic toxicity, the authors concluded that blood selenium concentrations alone are not an adequate monitor of selenium exposure or body burden at doses below chronic toxicity. It should be noted, however, that total body content and blood concentrations depend on daily intake of selenium. Since blood concentrations will vary as a reflection of daily selenium consumption, it may be more indicative of short-term exposure (Stewart et al. 1978).

Hamilton (1925) first reported selenium intoxication in an industrial setting. The incident occurred in a copper refining plant and the symptoms of the affected worker consisted of nasal pharyngitis and bronchitis. In addition, there were also symptoms of abdominal and lumbar pain and vomiting. The patient also noted a strong garlic odor on his breath. Following this report, there have been a number of reports confirming these symptoms as characteristic of selenium intoxication in industry. Additional symptoms described include: dermatitis, and neurological symptoms ranging from lightheadedness and giddiness to depression and emotional instability (Lemley 1940, Lemley and Merryman 1941).

Buchan (1947) reported an outbreak of selenium intoxication in a metal etching and imprinting plant which used ink containing selenium. Twenty workers had increased selenium levels in the urine and five developed symptoms of nausea, vomiting, metallic taste in the mouth, dizziness, extreme lassitude and fatigue. The air was found to be contaminated with less than 0.2 ppm (ppm units not defined), of hydrogen selenide and the symptoms ceased when a non-selenium ink was substituted.

Glover (1970) reviewed the industrial toxic effects of selenium and noted that in acute industrial intoxication, the symptoms first described by Hamilton (1925), i.e., nasal pharyngitis and bronchitis can be complicated by pulmonary edema. Glover states that thus far there has been no evidence of long-term systemic effects from selenium industrial intoxication. Nevertheless, Diskin et al. (1979) described a case of chronic pulmonary granulomatosis hypersensitivity in a patient who had been employed in a selenium refining plant for 50 years. Postmortem analysis of the lung, hair and nails revealed they contained excessive amounts of selenium.

4. Miscellaneous Studies

Kilness and Hochberg (1977) reported a cluster of four cases of amyotrophic lateral sclerosis (ALS) in a high-selenium environment and implied that there was a causal relationship. Nevertheless, clusters of ALS are noted to occur in areas in which there is a deficiency in selenium. The cases reported by Kilness and Hochberg occurred in South Dakota, which is known as a highly seleniferous region.

Westermarck (1977) reported a possible association between selenium deficiency and neuronal ceroid lipofuscinosis (NCL). He noted that vitamin E and selenium frequently work synergistically and observed that in patients with NCL that the vitamin E levels were low compared to normal subjects. He supplemented the diet of NCL patients with sodium selenite, and believed that he produced at least a transitory improvement without causing any toxic effects during a one-year period of administration. Whether selenium or vitamin E deficiency is related to this disease is at the most speculative.

Robertson (1970) considered the possible teratogenic effect of selenium. He reported on a five-year project involving ten women employed in a laboratory that prepared selenium containing culture media for *Salmonella*.

Two of the ten women were lost to followup. Of the remaining, six were married and two were single; four certain and one probable pregnancies occurred among these eight women. All ended in abortion except for one case which went to term, but the infant had bilateral club feet. This report is provocative and certainly should stimulate further investigation of the possible teratogenic effects of selenium in women who are exposed to the chemical, particularly in an industrial setting (See Section VI, D).

There are two epidemiologic studies in children which implicate selenium as being cariogenic (Hadjimarkos 1965, Tank and Storvick 1960). In these studies, children who ate food that contained an excess of selenium had a significant increase in the incidence of dental caries. These studies are supported by Buttner (1963) who noted a similar cariogenic role in his study of rats. He added selenium to the drinking water of pregnant rats and their offspring. There was a subsequent increase in caries in these rats proportional to the amount of selenium present. There was also a reduction in the number of young born.

H. Summary

It is the consensus from the scientific literature that selenium is an essential trace element for humans. The required intake for humans is approximately 50 to 200 μg/day (approximately 0.7 to 2.9 μg/kg/day based on a 70 kg human). Symptoms of selenium deficiency appear in individuals on a long-term selenium deficient diets, but disappear with selenium supplementation.

The recent discovery that cardiomyopathy (Keshan disease) occurs in selenium deficient humans in China confirms previous epidemiology studies which suggested a much higher incidence of cardiovascular disease with selenium deficiency and would indicate that selenium is indeed an essential trace element for humans.

In documented cases of industrial exposure resulting in acute selenium intoxication, signs of skin or mucous membrane irritation, and minor gastrointestinal symptoms have developed. Clear documentation of chronic selenium toxicity in humans has not been rigorously established. In high-selenium areas or in industrial situations where there is increased selenium exposure, there have been documented cases in which increased selenium blood concentrations were associated with symptoms ranging from vague malaise, pallor, fatigue, and gastrointestinal symptoms to a variety of skin, hair, tooth and nail lesions. Concentrations which produce symptomatology are ill-defined. Anecdotal evidence suggests that chronic human ingestion of 0.2 mg/kg-bw/day may be related to an increased incidence of these symptoms.

The relationship of selenium to human cancer remains open. However, the effect, if any, is most likely beneficial. While teratogenicity in humans remains a possibility, the only evidence of abnormality of the human fetus appears to rest on poorly documented reports. Mutagenicity has not been conclusively demonstrated in humans, however, a number of in vitro human cell culture tests have been positive for mutagenic effects. These results implicate various selenium compounds as a potential mutagen in humans.

VII. MECHANISMS OF TOXICITY

The mechanisms of selenium's toxic actions in the human and animal body are largely unknown. Some experiments which have pointed to selenium as an essential nutrient indicated that there was a third factor in the equation of selenium and vitamin E. This third factor was demonstrated by Rotruck et al. (1973) to be the enzyme glutathione peroxidase. Selenium was shown to be an integral part of the functional portion of the enzyme. The antioxidant properties, as well as the essential role of vitamin E (Evans and Burr 1927) for reproduction of rats, was well known. Tappel (1962) has advanced the hypothesis that antioxidants were necessary to prevent lipid peroxidation in tissue membranes. Although there was much skepticism at first, the notion that much of cellular injury is the result of free-radical formation with consequent lipid peroxidation and membrane damage involving all classes of cellular membranes is gaining widespread acceptance. The classical model of tissue injury in the liver, CCl_4, is now largely accepted as being due to free-radical formation and lipid peroxidation. Thus, glutathione peroxidase has assumed greater importance as a defense mechanism, and selenium deficiency could be a factor. Whether selenium excesses, either acute or chronic, could affect the function of this system is unknown.

It has been demonstrated that glutathione peroxidase is the principal means for removing hydrogen peroxide in erythrocytes (Cohen and Hockstein 1963). Since the glutathione peroxidase level is closely governed by the intake of selenium, it appears that the ability of selenium to reduce susceptibility of erythrocytes to hemolysis is largely mediated through this selenoenzyme. It would therefore appear that lipid peroxidation is a very common mechanism of tissue damage through its alterations in membrane structure. This leads to ion shifts and altered permeability which can be prevented by the antiperoxidative action of vitamin E (α-tocopheral) and glutathione peroxidase (Diplock 1976b).

The mechanism by which excess selenium produces toxicity is largely unknown. It is evident that a variety of inorganic selenium compounds can be converted to selenious acids, and thus the irritative properties of direct contact (nasal, oral, ophthalmic mucosa) are probably mediated through hydrogen ion released in the aqueous tissue environment. Selenium can substitute for sulfur in most reactions, including being incorporated into protein (Stadtman 1979). Thus, in chronic exposure, its toxicity is generally assumed to be due to its interference with sulfur metabolism (Venugopal and Luckey 1977) and the organism's inability to distinguish between selenium and sulfur (Hausknecht and Ziskind 1976). Its ability to antagonize arsenic, cadmium, mercury, silver and lead toxicity is described previously in the document (Section V), however, the mechanisms are largely unknown.

The observation that selenium appears to have an anticarcinogenic effect has also been discussed previously (Sections V, VI). The mechanism of this action is entirely speculative. While it is reasonable to suppose that this may again be related to membrane effects, there is no hypothesis with sufficient proof to warrant extensive discussion.

From these brief remarks it is evident that the mechanism of action of selenium is an important area for further investigation. It appears to be essential in the diet, perhaps because of its role in the enzyme glutathione peroxidase. The mechanism of its toxicity remains to be elucidated, with the possible exception that its acute irritative effects are due to selenious acid production and direct tissue destruction.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Acceptable Daily Intake (ADI) is calculated. From this an Adjusted Acceptable Daily Intake (AADI) and Health Advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{(\text{NOAEL or LOAEL in mg/kg/day})(\text{Body Weight in kg})}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking Water Volume in L/day}} = \text{mg/L}$$

where:

NOAEL = no-observed-adverse-effect level.

LOAEL = lowest-observed-adverse-effect level.

Body weight = 70 kg for adult or 10 kg for child.

Drinking water volume = 2 L per day for adults or 1 L per day for children.

Uncertainty/Safety Factor = 10, 100 or 1,000.

Utilizing these equations, the following drinking water concentrations are developed for non-carcinogenic effects:

1. A one-day HA for 10-kg child.
2. A one-day HA for 70-kg adult.
3. A ten-day HA for 10-kg child.
4. A ten-day HA for 70-kg adult.
5. A lifetime AADI for a 70-kg adult.

The distinctions made between the HA calculations (items 1 through 4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1 to 2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon non-carcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS 1977, 1980a) is typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data identifying a NOEL/NOAEL are available and are supported by acute or chronic toxicity data in other species.

- An uncertainty factor of 100 is used either when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more animal species (but human data are not available), or when good acute or chronic toxicity data identifying a LOAEL in humans are available.

- An uncertainty factor of 1,000 is used either when limited or incomplete acute or chronic toxicity data are available, or when good acute or chronic toxicity data identify a LOAEL (but not a NOEL/NOAEL) for one or more animal species.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines for selection of an uncertainty factor, but must be considered include: (1) the quality of the toxicology data, (2) the significance of the adverse effect and (3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (there is insufficient evidence to classify selenium as a carcinogen following oral exposure), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical via drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans from these data, it must be converted to an equivalent human dose. This conversion includes correction for non-continuous animal feeding, non-lifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 liters of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as (1) incomplete knowledge concerning the health effects of contaminants in drinking water, (2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results and (3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

A. Non-Carcinogenic Effects

1. Toxic Effects

Selenium (Se) may assume four oxidation states (2^-, 0, 4^+, 6^+). The selenates (6^+) are the most readily soluble in water; thus, these compounds would be of primary concern in drinking water. Heavy metal selenides (2^-) are insoluble, as is the elemental form (0). The inorganic selenites (4^+) form stable absorption complexes with iron and aluminum compounds and are reduced to elemental selenium in acidic and reducing conditions.

Toxicity studies have been carried out on selenium compounds of the various oxidation states. The results of these studies have shown the toxicities of selenate and selenite to be fairly similar (Palmer and Olson 1974). A substantial susceptibility differential among animal species has not been noted for selenium.

Selenium has been shown to exhibit toxic effects at high dose levels in animals. In livestock, excess selenium intake produces an acute syndrome known as "blind staggers" disease. In this disease, the animal exhibits impaired vision, difficulty in judging the closeness of objects, abdominal pain and paralysis. Sodium selenite and selenate have been tested for acute toxicity in laboratory animals. The minimum lethal dose of sodium selenite (mg Se/kg-bw) was reported to be 3.0 to 5.7 for the rat by the subcutaneous route, 0.9 to 1.5 for the rabbit by intravenous injection and 2.0 for the dog by intraperitoneal injection (Moxon and Rhian 1943).

Chronic toxicity of selenium in animals results in a disorder known as "alkali disease." This disease is characterized by hair loss and deformation of the hooves in livestock, lesions of internal organs, glomerulonephritis and anemia.

Several studies investigating the chronic effects of selenium have been carried out in laboratory animals. Harr et al. (1967) fed sodium selenite and selenate daily to rats at levels up to 16 mg Se/kg of feed. Rats fed 0.5 mg Se/kg of feed for two years showed normal growth and lived as long as controls, while those at a dose of 4 mg Se/kg of feed (two years) grew slowly, and only 10% survived 15 to 24 months. Harr and Muth (1972) summarized the findings of Harr et al. (1967) and concluded that the minimal toxic level was 0.75 mg Se/kg of feed based on longevity and lesions in the heart, kidneys and spleen and 0.25 mg Se/kg of feed based on pathologic changes in the liver. Thus, the LOAEL was 0.03 mg/kg-bw/day (assuming 0.01 kg-bw and 0.01 kg feed/day) based on hepatopathology observed in rats fed 0.25 mg Se/kg of feed.

In a study by Halverson et al. (1966), young male rats were fed sodium selenite or naturally occurring selenium diets for six weeks. The dietary level of selenium was 1.6, 3.2, 4.8, 6.4, 8.0, 9.6 or 11.2 mg/kg of diet. This corresponds to an average daily dose of 0.14, 0.28, 0.41, 0.55, 0.68, 0.81 or 0.95 mg Se/kg-bw, assuming a mean body weight of 0.15 kg and dietary consumption of 0.013 kg/day for the 1.6- to 6.4-ppm diet groups and a mean body weight of 0.13 kg and dietary consumption of 0.011 kg for the 8.0- to 11.2-ppm diet groups. At selenium concentrations of 1.6, 3.2 or 4.8 ppm, no significant effect on growth was noted as determined by the responses of the treated and control animals, although a small growth depression was observed with the group that received 4.8 mg Se/kg as sodium selenite. Growth was affected at selenium concentrations of 6.4 mg/kg (0.55 mg Se/kg-bw/day) of selenium-containing grain, and the spleens of the treated animals were significantly enlarged ($P<0.01$) as compared to those of the control animals. Macroscopic examination revealed roughness, mottling and discoloration of the livers. At selenium concentrations above 8.0 mg/kg of feed (0.68 mg Se/kg-bw/day), increased mortality, enlargement of the spleen and pancreas, reduced liver-to-body weight ratios and decreased blood hemoglobin were observed. Thus, the dietary intake of 4.8 mg/kg of feed (0.41 mg Se/kg-bw/day) was the NOAEL identified by this study.

Palmer and Olson (1974) administered 2 mg/L sodium selenite and 3 mg/L sodium selenate in the drinking water of rats for six weeks. Neither concentration produced mortality, although a slight decrease in growth was noted. At concentrations of 6 mg/L and 9 mg/L (sodium selenite and sodium selenate), the mortality was high; 5 out of 12 rats died at the lower dose, and 11 out of 12 rats died at the higher dose.

In a study by Nelson et al. (1943), rats received selenium at levels of 5, 7 and 10 ug/g of diet. Mortality was high at all doses; only 53 of the 126 selenium-fed rats survived for 18 months, and only 39 survived for 24 months.

In humans, few cases of acute oral toxicity of selenium have been reported. Carter (1966) discussed a case in which a child drank gun-blueing compound containing selenious acid (Se concentration unspecified). Clinical signs of acute toxicity included peripheral vascular collapse, pulmonary edema and coma, with the autopsy revealing pulmonary congestion, hemorrhage and edema.

Chronic toxicity of selenium ingested in the diet was reported in some early studies on seleniferous areas in the United States. Smith et al. (1937) examined dietary intake and excretion of selenium in farmers in seleniferous areas and reported suggestive evidence that chronic selenium ingestion (levels unknown) may result in general lassitude, pallor, fatigue and other non-specific systemic symptoms. It is unclear whether these symptoms were the direct result of the selenium exposure.

Only one case of human selenium toxicity directly attributable to a water source has been reported. A family was exposed for approximately three months to well water containing 9 mg Se/L. A reported loss of hair, weakened nails, listlessness and general lack of mental alertness were observed. The symptoms appeared to be reversible; the children showed increased mental alertness, as measured by better performance in school, after use of the water from the seleniferous well was discontinued (Rosenfeld and Beath 1964).

Yang et al. (1983) examined endemic selenium intoxication in humans in China. The report documented at least four levels of selenium consumption in humans: high selenium with chronic selenosis, high selenium in the absence of selenosis, selenium adequate and low selenium manifested by Keshan disease. The daily dietary intake of selenium averaged 4.99 mg/day for the group with chronic selenosis. The minimum daily dietary selenium intake for the group from the geographic area with endemic chronic selenosis was 3.20 mg/day. This minimum dietary intake of selenium is considered the LOAEL and corresponds to a daily dose of 0.046 mg/kg for a 70-kg adult. For the group in the high selenium area without selenosis, a mean daily intake of 0.75 mg was reported, with a maximum level of 1.51 mg/day.

2. Nutritional Requirements

Selenium deficiency has been associated with congenital white muscle disease and nutritional myopathy in lambs and calves. In livestock, insufficient selenium intake has also been implicated as the cause of a group of diseases, including muscular weakness of the newborn, immunosuppression, reduced weight gain and infertility (Van Vleet 1980).

In general, the dietary requirements for selenium of mammalian species appear to be at a level of 0.1 mg Se/kg of food (NAS 1971, 1980). In cattle, addition of sodium selenite to a salt-mineral mixture has been shown to be a highly practical method of treating selenium deficiency (Koller et al. 1983). In the chicken, selenium prevents pancreatic degeneration; the level necessary to prevent this effect appears to be dependent on the dietary level of vitamin E (Thompson and Scott 1970). A deficiency of selenium has been shown to produce hepatic necrosis in rats, exudative diathesis in poultry, hepatosis dietetica in swine and skeletal muscle degeneration in poultry, domestic animals and laboratory animals (Diplock 1976a).

Selenium is considered to be an essential element for human nutrition. In patients on total parenteral nutrition in the absence of selenium supplementation, muscle discomfort and stiffness have been reported. Supplementation of the total parenteral nutrition with selenium relieved the symptoms. Keshan disease, a cardiac disease characterized by heart failure, cardiac enlargement and abnormalities of the EKG, has occurred predominantly in women of child-bearing ages and in children in the People's Republic of China. Supplementation of the diet with sodium selenite appeared to prevent or reverse the disease (Van Rij et al. 1979). As previously described, a study by Yang et al. (1983) examined selenium intoxication in humans in China. In this study, it was reported that the average daily selenium intake in the low selenium area where Keshan disease occurred was 0.011 mg, with a maximum level of 0.022 mg. Chronic selenium deficiency has also been alleged to cause muscle weakness and stiffness in people residing in selenium-deficient areas of New Zealand (Thompson and Robinson 1980). These results are subjective and have not been confirmed.

For humans, an intake of about 0.1 to 0.2 μg Se/g of diet (based upon animal requirements) appears to be an adequate maintenance level for adults. This translates to a daily intake of 100 to 200 μg for a 70-kg adult consuming 1 kg of diet (dry basis) per day (NAS 1980b). Human studies indicate that a total intake of 60 to 120 μg/day of selenium appears to be adequate to prevent deficiency (Levander 1976). The Food and Nutrition Board of the National Research Council (NAS 1980b) has recommended a safe and adequate selenium intake of 50 to 200 μg/day for adults and lower levels for infants and children (see Table VIII-1). The average adult intake of selenium in this country appears to be in the range of 100 to 200 μg/day (see Section IV).

B. Quantification of Non-Carcinogenic Effects

In the quantification of non-carcinogenic effects for selenium, it is necessary to consider both the upper and lower levels of the chemical that would elicit neither toxicity nor deficiency effects.

1. One-Day Health Advisory

Insufficient data exist to calculate one-day HA values for selenium. The available information on acute toxicity consists of data on lethal doses and

Table VIII-1. Recommended Estimated Adequate and Safe Intakes.[a]

Group	Age (years)	Estimated adequate and safe total daily intakes of selenium (mg/day)
Infants	0-0.5	0.01-0.04
	0.5-1	0.02-0.06
Children	1-3	0.02-0.08
	4-6	0.03-0.12
	7-10	0.05-0.2
	11+	0.05-0.2
Adults	--	0.05-0.2

[a] According to the NAS, these values represent an estimate of an adequate total daily intake of selenium. Any daily intakes within the ranges recommended are considered to be adequate and safe, and the recommendations do not imply that the intakes at the upper limit of the range are more desirable or beneficial than those at the lower limit. In addition, these ranges do not imply that values above the upper limits represent toxic levels of selenium.

Adapted from NAS (1980b).

does not provide the dose-response data that are needed in the calculation of the one-day HA values for the 10-kg child or 70-kg adult. Therefore, the values calculated for the ten-day HA (below) will be taken as conservative estimates of the appropriate one-day values.

2. Ten-Day Health Advisory

In the calculation of ten-day HA values for the 10-kg child and the 70-kg adult, it is necessary to use subchronic data from which a LOAEL or a NOAEL can be determined. In the Halverson et al. (1966) study, rats were fed sodium selenite for six weeks, and levels of 4.8 mg/kg feed (daily dose of 0.41 mg Se/kg-bw) produced no significant adverse effects as compared with controls.

The ten-day HA for the 10-kg child is calculated as follows:

Ten-Day Health Advisory for Child:

$$\frac{(0.41\text{ mg/kg/day})\ (10\text{ kg})}{(1\text{ L/day})\ (100)} = 0.041\text{ mg/L }(41\text{ ug/L})$$

where:

0.41 mg/kg/day = NOAEL, based on absence of growth depression, pathological changes in the liver and enlargement of the spleen in rats fed sodium selenite for six weeks (Halverson et al. 1966).

10 kg = assumed weight of child.

1 L/day = assumed water consumption by a 10-kg child.

100 = uncertainty factor. This uncertainty factor was selected in accordance with ODW/NAS guidelines in which a NOAEL from an animal study is employed.

The ten-day HA for the 70-kg adult is calculated as follows:

Ten-Day Health Advisory for Adult:

$$\frac{(0.41 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})\ (100)} = 0.144 \text{ mg/L } (144 \text{ ug/L})$$

where:

0.41 mg/kg/day = NOAEL, based on absence of growth depression, pathological changes in the liver and enlargement of the spleen in rats fed sodium selenite for six weeks (Halversen et al. 1966).

70 kg = assumed weight of adult.

2 L/day = assumed water consumption by a 70-kg adult.

100 = uncertainty factor. This uncertainty factor was selected in accordance with ODW/NAS guidelines in which a NOAEL from an animal study is employed.

These calculations result in selenium exposures through the drinking water that are above the NAS' safe and adequate range for the adult (50 to

200 µg/day) and within the range for the child (20 to 80 µg/day). Thus, deficiency effects would not be exhibited at these levels, and an adequate margin of safety is provided to protect against toxic effects.

3. Adjusted Acceptable Daily Intake

Chronic toxicity studies in animals and humans indicate that the LOAEL ranges from 0.03 to 0.05 mg/kg-bw/day. The ADI derived on the basis of human data is used to establish the AADI. An ADI calculated on the basis of animal data is provided for comparison.

a. ADI Calculation Based Upon Animal Data

In the calculation of a lifetime AADI, a chronic study with good dose-response data should be used. The Halverson et al. (1966) and Palmer and Olson (1974) studies will not be used to calculate an AADI due to the fact that these were not chronic studies; both were of six weeks' duration. The Nelson et al. (1943) study will not be used to calculate an AADI due to the high mortality among the rats at all dose levels.

The Harr et al. (1967) study identifies a LOAEL that will be used to calculate an ADI. The assumption will be made that the animal and human absorption rates are identical; thus, the absorption rate will not be factored into the analysis.

Harr et al. (1967) fed sodium selenite and selenate daily to rats for two years. The lowest dose at which adverse health effects were noted was 0.25 mg Se/kg of feed (initial daily dose of 0.03 mg/kg-bw). At this dose, pathologic changes were noted in the liver.

The ADI for a 70-kg adult is calculated as follows:

ADI:

$$\frac{(0.03 \text{ mg/kg/day})\ (70 \text{ kg})}{(1{,}000)} = 0.002 \text{ mg/day } (2 \text{ ug/day})$$

where:

0.03 mg/kg/day = LOAEL, based on hepatopathologic effects in rats exposed to selenite and selenate via food for two years (Harr et al. 1967).

70 kg = assumed weight of adult.

1,000 = uncertainty factor. This uncertainty factor was selected in accordance with ODW/NAS Guidelines in which a LOAEL from an animal study is employed.

b. ADI Calculations Based Upon Human Data

Yang et al. (1983) examined chronic selenosis in humans. Selenosis occurred in humans with an average daily selenium intake of 4.99 mg. The minimum daily selenium intake level reported in the geographic area with endemic chronic selenosis was 3.20 mg. Using 3.20 mg/day as a LOAEL, an ADI may be calculated.

The ADI for a 70-kg adult is calculated as follows:

ADI:

$$\frac{3.20\ \text{mg/day}}{15} = 0.213\ \text{mg/day}\ (213\ \mu\text{g/day})$$

where:

3.20 mg = minimum daily selenium intake level (dietary) in area of chronic selenosis (Yang et al. 1983).

15 = uncertainty factor. This uncertainty factor was based upon a human study identifying the LOAEL. According to the ODW/NAS guidelines, when a human study with a LOAEL is used, the ADI is calculated using an uncertainty factor of 100. In this instance, however, an uncertainty factor of 15 was applied due to the fact that a large amount of data exists which indicate the severity of deficiency effects from selenium as well as the anti-carcinogenic properties of selenium. Thus, an uncertainty factor of 15 appears to be adequate to provide a balance between the adverse and beneficial effects of selenium in humans. In addition, data exist which suggest that selenium ingested in food may be absorbed less efficiently than

selenium ingested in water. Concurrent ingestion of food was shown to decrease the absorption of several heavy metals from the gastrointestinal tract (Rabar and Kostral 1981). This information would support the use of an uncertainty factor greater than 10, since the Yang et al. (1983) study was based upon selenium exposure from food only.

c. AADI Calculations

The ADI based upon human data will be used to calculate an AADI because human data are more representative of the human condition than are animal data.

Using the ADI of 213 ug/day (based upon human data) and assuming the 70-kg adult consumes two liters of drinking water per day, the AADI is calculated as follows:

AADI:

$$\frac{(213\ \mathrm{ug/day})}{(2\ \mathrm{L/day})} = 0.106\ \mathrm{mg/L}\ (106\ \mathrm{ug/L})$$

where:

213 ug/day = ADI based upon human data from the Yang et al. (1983) study.

2 L/day = Assumed water consumption for 70-kg adult.

This AADI calculation assumes that 100% of the human exposure derives from drinking water. This value may be modified upon the availability of relative source contribution data that provide estimates of human exposure from food, air and possibly the occupational environment.

C. Carcinogenic Effects

Six long-term research studies investigating the carcinogenic potential of selenium have been carried out. Only one, the study by Nelson et al. (1943), showed an increase in tumor incidence in selenium-fed animals as compared to controls. Nelson et al. (1943) fed rats 5, 7 or 10 µg Se/g of diet for two years. A total of 126 rats were exposed to selenium, and 18 served as controls. Of 51 rats that survived at least 24 months, 11 developed liver tumors diagnosed as hepatic cell adenomas or low grade hepatic cell carcinomas. Four others had pronounced adenomatoid hepatic cell hyperplasias that could be interpreted as a transition to tumor. In the 73 selenium-treated rats that died or were sacrificed before 18 months, there were no tumors and no advanced adenomatoid hyperplasia, although cirrhosis was frequent. The 14 control rats that lived at least 18 months had neither adenomatous nor neoplastic lesions nor cirrhosis.

Subsequent investigations have failed to demonstrate an increased tumor incidence in animals following exposure to selenium as selenate or selenite. Harr et al. (1967) and Tinsley et al. (1967) fed selenium at levels ranging from 0.5 to 16 µg/g as dietary sodium selenite and sodium selenate. Acute toxic hepatitis was observed in animals receiving selenium in the diet at the concentration of 4, 6, 8 or 16 μg/g and in the commercial diet with 16 μg/g of added selenium. No hepatic neoplasms were observed among the selenium-exposed animals. Harr et al. (1967) concluded that neoplasia in rats is not induced by selenite, selenate or methionine and selenate combined.

The National Cancer Institute carried out a chronic bioassay on selenium sulfide in six-week-old male and female mice and rats by gavage (NCI 1980). Dose levels of 20 or 100 mg/kg selenium sulfide were administered in mice, and levels of 3 or 15 mg/kg were administered in rats. Decreased body weight and increased tumor formation were observed in female mice and in rats of both sexes. An increased incidence of hepatocellular carcinomas and adenomas was reported in dosed rats and female mice. Dosed female mice also had an increased incidence of alveolar/bronchiolar carcinomas and adenomas. The study concluded that selenium sulfide was carcinogenic for rats and mice, inducing hepatocellular carcinomas in rats and female mice and alveolar/bronchiolar carcinomas and adenomas in female mice.

Selenium sulfide is a manufactured product, which is not normally found in water, and these results do not indicate that naturally occurring selenium compounds (selenite or selenate) are carcinogenic.

The NAS (1976) has concluded that despite an initial report of selenium as a carcinogen, subsequent investigations have demonstrated that chronic experimental exposure of rats and mice to selenium (selenite or selenate) has not induced neoplasia. The International Agency for Research on Cancer (IARC) has concluded that available animal data are insufficient to allow an evaluation of the carcinogenicity of selenium compounds (IARC 1975). The Commissioner of the Food and Drug Administration has concluded that the available information does not support classification of selenium or its compounds as having carcinogenic activity and that the available animal data are insufficient to allow an evaluation of the carcinogenicity of selenium compounds (FDA 1974).

D. Anticarcinogenic Effects

Selenium supplementation has been shown to result in the inhibition of tumors of various types, including tumors of the skin, liver, mammary glands, colon and lung. It has been postulated that selenium inhibits the promotion phase of carcinogenesis. Upon withdrawal of the selenium supplement, tumors will emerge at the same rate as those in selenium-untreated animals.

There is presently no evidence that naturally occurring selenium compounds encountered in drinking water are carcinogenic in humans. On the contrary, epidemiological studies have suggested that selenium may be protective against human cancer. An inverse relationship has been reported to exist between cancer death rates and selenium concentrations in vegetation in selected areas in the United States and Canada (Shamberger and Willis 1971, Schrauzer et al. 1976). The IARC (1975) has concluded, "The available data provide no suggestion that selenium is carcinogenic in man, and the evidence for a negative correlation between regional cancer deaths and selenium is not convincing."

Several studies have shown cancer patients to have lower blood selenium levels than healthy individuals, but these studies have been based entirely on selenium measurements made after diagnosis. Willett et al. (1983) examined and compared selenium levels in serum samples collected in 1973 from 111 subjects in whom cancer developed during the subsequent five years with those in serum samples from 210 cancer-free subjects matched for age, race, sex and smoking history. The mean selenium level of cases was significantly lower than that of controls. Thus, there appears to be some evidence in humans that low selenium intake is correlated with an increased risk of developing cancer. However, the magnitude of the effect, the cancer sites and the high risk population remain to be defined.

E. Quantification of Carcinogenic Effects

Naturally occurring selenium (selenite or selenate) is not considered to be an animal or human carcinogen, and thus, excess carcinogenic risk values have not been calculated for the compound.

F. Existing Guidelines and Standards

The existing standard for selenium in drinking water under the National Interim Primary Drinking Water Regulations is 10 µg/L. The World Health Organization (WHO) has recommended a selenium action level of 10 µg/L. The WHO did not provide a rationale for recommending this level.

The USEPA ambient water quality criterion for selenium is 10 µg/L (USEPA 1980), identical to the existing drinking water standard. This value was calculated based upon an acceptable daily intake of Se from foods of 0.7 mg and a drinking water contribution of 5% to 10% of the dietary level. A maximum water-related contribution of 35 µg Se/day was selected as protective, and consumption of 6.5 g fish was factored in. A criterion level of 16.6 µg Se/L was calculated, with a final value of 10 µg proposed for the reasons that, "it appears that the USEPA Drinking Water Standard of 10 µg/L is probably an appropriate ambient criterion level to protect the health of the US population."

There are several reasons why the AADI differs from the ambient water quality criteria level. The AADI was based upon a recently completed human study, while the water quality criteria level was based upon animal data. The water quality criteria did not consider the nutritional requirements for selenium, while the proposed AADI considered the essentiality of the compound.

G. Special Considerations

1. High Risk Populations

The developing fetus may be at higher risk from excess selenium exposure than is the general population. Selenium has been shown to be teratogenic in certain animal species at high dose levels, and there have been case reports of teratogenicity in range animals on seleniferous feeds. In light of this information, the human fetus may be at higher risk from excess selenium exposure than is the general population. It is not possible to factor this information into the risk assessment due to the many unknown factors involving this sensitive subpopulation and the fact that it is not possible to quantify exposure.

2. Interactions

Selenium has been shown to have interactive effects with a large number of compounds. Selenium has been shown to be antagonistic to the toxic effects of silver, arsenic, cadmium and mercury. Sulfate and vitamin E combined with methionine have been shown to be antagonistic to the toxic effects of selenium. This information was not factored into the risk assessment because it is not possible to quantify these interactions.

3. Beneficial Effects

Selenium is an essential element for human nutrition. Dietary selenium deficiency was associated with Keshan disease in humans. Selenium supplementation may prevent or reverse Keshan disease. Data indicate that selenium may have anti-carcinogenic properties and that deficiency may be related to increased risk for cancer in humans. The beneficial effects of selenium and severity of adverse effects due to deficiency were considered in establishing the uncertainty factor used in the AADI calculation.

H. Summary

The recommended one-day and ten-day HA values for both adults and children and the AADI are summarized in Table VIII-2.

Table VIII-2. Summary of Quantification of Toxicological Effects.

	Drinking water concentration (mg/L)		
	10-kg child	70-kg adult	Reference[a]
One-Day Health Advisory	0.041[b]	0.144[b]	Halverson et al. (1966)
Ten-Day Health Advisory	0.041	0.144	Halverson et al. (1966)
AADI	--[c]	0.106	Yang et al. (1983)

[a] Reference for NOAEL or LOAEL used in calculation of HA or AADI values.

[b] Ten-day HA values were taken to be conservative estimates of appropriate one-day values since no appropriate data for calculation of one-day HA values were found.

[c] Not calculated because the AADI is based on lifetime exposure.

IX. REFERENCES

ACGIH. 1977. American Conference of Government Industrial Hygienists. Threshold limit values for chemical substances in workroom air adopted by ACGIH for 1977.

Allaway WH, Kubota J, Losee F, et al. 1968. Selenium, molybdenum and vanadium in human blood. Arch. Environ. Health 16:342-348.

Ammerman CB. 1981. Selenium. Amer. Nutr. Health April:22-27.

Arnold RL, Olson OE, Carlson CW. 1973. Dietary selenium and arsenic additions and their effects on tissue and egg selenium. Poult. Sci. 52:847-854.

Awasthi YC, Butler E, Srivastava SK. 1975. Purification and properties of human erythrocyte glutathione peroxidase. J. Biol. Chem. 250:5144-5149.

Banner WP, Tan QH, Zedeck MS. 1982. Selenium and the acute effects of carcinogens, 2-acetylaminofluorene and methylazomethanol acetate. Cancer Res. 42:2985-2989.

Beath OA, Eppson HF, Gilbert CS, Bradley WB. 1939. Poisonous plants and livestock poisoning. Wyoming Agr. Expt. Station Bull. No. 231:1-104.

Benavides ST, Mojica RFS. 1959. Seleniosis ocurrencia de selenio en rocas suelos y plantas. Intoxicacion por selenio en animales y en humanos. Publicacion I T-3, Instituto Geografico de Colombia, Bogota, Columbia.

Besbris HJ, Wortzman MS, Cohen AM. 1982. Effect of dietary selenium on the metabolism and excretion of 2-acetylaminofluorene in the rat. J. Toxicol. Environ. Health 9:63-76.

Birkner JH. 1978. Selenium in aquatic organisms from seleniferous habitats. Doctoral dissertation. Colorado State University, Morgan Library, Fort Collins, Colorado. p. 121.

Boyne R, Arthur JF. 1979. Alterations of neutrophil functions in selenium-deficient cattle. J. Comp. Path. 89:152-158.

Broghamer WL Jr., McConnell KP, Blotcky AJ. 1976. Relationship between serum selenium levels and patients with carcinoma. Cancer 37:1384-1388.

Broghamer WL Jr., McConnell KP, Grimaldi M, Blotcky AJ. 1978. Serum selenium and reticuloendothelial tumors. Cancer 41:1462-6.

Browne CL, Dumont JN. 1979. Toxicity of selenium to developing *Xenopus laevis* embryos. J. Toxicol. Environ. Health 5:699-709.

Browne CL, Dumont JN. 1980. Cytotoxic effects of sodium selenite on tadpoles (*Xenopus laevis*). Arch. Environ. Contam. Toxicol. 9:181-91.

Browning E. 1969. Toxicity of industrial metals. 2nd. ed. Appleton-Century-Crofts, New York. pp. 286-295.

Buchan RF. 1947. Industrial selenosis. A review of the literature, report of five cases and a general bibliography. Occup. Med. 3:439-456.

Burk RF. 1976. The significance of selenium levels in blood. Proceedings of the Symposium on Selenium-Tellurium in the Environment. Industrial Health Foundation, Inc., Pittsburgh, Penn. pp. 194-203.

Burk RF. 1978. Selenium in nutrition. World Rev. Nutr. Diet. 30:88-106.

Buttner W. 1963. Action of trace elements on the metabolism of fluoride. J. Dent. Res. 42:453-460.

Byard JL. 1968. The metabolism of sodium selenite in the rat. Ph.D. dissertation. University of Wisconsin, Madison. p. 87.

Bycroft BM, Clegg DE. 1978. Gas-liquid chromatographic determination of selenium in biological materials, using 4-bromo and 4-chloro 1,2- diaminobenzene as derivatizing reagents. J. Assoc. Off. Anal. Chem. 61:923-926.

Carter RF. 1966. Acute selenium poisoning. Med. J. Aust. 1:525.

Cawley GD, Bradley R. 1978. Sudden death in calves associated with acute myocardial degeneration and selenium deficiency. Vet. Rec. 103:239-240.

Chapco W, Jones SG, McConnell WB. 1978. Correlations between chromosome segments and fitness in Drosophila melanogaster. III. Differential genetic responses to.zinc, sulfate and selenocystine. Can. J. Genet. Cytol. 20:555-565.

Chappell WR. 1979. Heavy metal pollution from shale oil production. International Conf. of Heavy Metals in the Environment (London) pp. 592-595.

Chau YK, Wong PTS, Silverberg BA, Luxon PL, Bengert GA. 1976. Methylation of selenium in the aquatic environment. Science 192:1130-1131.

Cherkes LA, Aptekar SG, Volgarev MN. 1962. Hepatic tumors of the liver caused by selene. Bull. Eksp. Biol. Med. 53:78-83. (In Russian; translation)

Clayton CC, Baumann CA. 1949. Diet and azo dye tumors: effect of diet during a period when the dye is not fed. Cancer Res. 9:575-582.

Clegg DJ. 1971. Embryotoxicity of chemical contaminants of foods. Food Cosmet. Toxicol. 9:195-205.

Clement IP. 1981. Prophylaxis of mammary neoplasia by selenium supplementation in the initiation and promotion of chemical carcinogens. Cancer Res. 41:4386-4390.

Cohen G, Hochstein, P. 1963. Glutathione peroxidase: the primary agent for the elimination of hydrogen peroxide in erythrocytes. Biochemistry 2:1420.

Cummins LM, Kimura ET. 1971. Safety evaluation of selenium sulfide antidandruff shampoos. Toxicol. Appl. Pharmacol. 20:89-96.

Daoud AH, Griffin AC. 1978. Effects of selenium and retinoic acid on the metabolism of N-acetylaminofluorene and N-hydroxyacetylaminofluorene. Cancer Lett. 5:231-237.

Daoud AH, Griffin AC. 1980. Effect of retinoic acid, butylated hydroxytoluene, selenium and sorbic acid on azo-dye hepatocarcinogenesis. Cancer Lett. 9:299-304.

De Geoij JJ, Guinn VP, Young DR, Mearns AJ. 1974. Neutron activation analysis trace element studies of Dover sole liver and marine sediments. In: Comparative studies of food and environmental contamination. International Atomic Energy, Vienna, Austria pp. 189-200.

Desowitz RS, Barnwell JW. 1980. Effect of selenium and dimethyl dioetadecyl ammonium bromide on the vaccine-induced immunity of Swiss-Webster mice against malaria. Infect. Immun. 27:87-89.

Diplock AT. 1976a. Metabolic aspects of selenium action and toxicity. CRC Crit. Rev. Toxicol. 4:271-329.

Diplock AT. 1976b. The tocopherol-selenium interaction. Proceedings of the Symposium on Selenium-Tellurium in the Environment. Industrial Health Foundation, Inc., Pittsburgh, Penn. p. 158-177.

Diplock AT, Green J, Bunyan J, McHale P, Muthy IR. 1967. Vitamin E and stress 3. The metabolism of D-α-tocopherol in the rat under dietary stress with silver. Br. J. Nutr. 21:115-125.

Diskin CJ, Tomasso CL, Alper JC, Glaser ML, Fliegel SE. 1979. Long-term selenium exposure. Arch. Intern. Med. 139:824-6.

Dubois KP, Moxon AL, Olson OE. 1940. Further studies on the effectiveness of arsenic in preventing selenium poisoning. J. Nutr. 19:447-482.

Dudley HC. 1936. Toxicology of selenium. I. A study of the distribution of selenium in acute and chronic cases of selenium poisoning. Am. J. Hyg. 23:169-180.

Dudley HC. 1938. Toxicology of selenium. V. Toxic and vesicant properties of selenium oxychloride. U.S. Pub. Health Rep. 53:94-98.

Eggleston LV, Krebs HA. 1974. Regulation of the pentose phosphate cycle. Biochem. J. 138:425-435.

Evans HM, Burr GO. 1927. The antisterility vitamine fat soluble E. Memoirs of the University of California. Vol. 8. Berkeley, California: Univ. of Cal. Press.

Exon JH, Koller LD, Elliott SC. 1976. Effect of dietary selenium on tumor induction by an oncogenic virus. Clin. Toxicol. 9:273-279.

FDA. 1974. Food and Drug Administration. Rule making on selenium in animal feeds. Bureau of Veterinary Medicine, Rockville, Md.

FDA. 1980a. Food and Drug Administration. FDA compliance program report of findings. FY 1977 total diet studies -- adult (7320.73). Washington, DC: U.S. Department of Health, Education, and Welfare.

FDA. 1980b. Food and Drug Administration. FDA compliance program report of findings. FY 1977 total diet studies -- infants and toddlers (7320.74). Washington, DC: U.S. Department of Health, Education, and Welfare.

FDA. 1982a. Food and Drug Administration. FDA compliance program report of findings. FY 79 total diet studies -- adult (7305.002). Washington, DC: U.S. Department of Health and Human Services.

FDA. 1982b. Food and Drug Administration. FDA compliance program report of findings. FY 79 total diet studies -- infants and toddlers (7305.002). Washington, DC: U.S. Department of Health and Human Services.

Fishbein L. 1977. Toxicology of selenium and tellurium. Adv. Mod. Toxicol. 2:191-240.

Flohe L, Gunzler WA, Schock HH. 1973. Glutathione peroxidase: a selenoenzyme. Fed. Eur. Biochem. Soc. Lett. 32:132-134.

Forstrom JW, Zakowski JJ, Tappel AL. 1978. Identification of catalytic site of rat liver glutathione peroxidase as selenocysteine. Biochemistry 17:2623.

Franke KW, Moxon AL. 1936. A comparison of the minimum fatal doses of selenium, tellurium, arsenic, and vanadium. J. Pharmacol. Exp. Ther. 58:454-457.

Franke KW, Moxon AL, Poley WE, Tully WC. 1936. Monstrosities produced by injection of selenium salts into hens' eggs. Anat. Rec. 65:15-22.

Franke KW, Potter VR. 1935. A new toxicant occurring naturally in certain samples of plant foodstuffs. IX. Toxic effects of orally ingested selenium. J. Nutr. 10:213-221.

Franke KW, Potter VR. 1936. A new toxicant occurring naturally in certain samples of plant foodstuffs. XIII. The ability of rats to discriminate between diets of varying toxicity. Science 83:330-332.

Ganther HE. 1966. Enzymic synthesis of dimethyl selenide from sodium selenite in mouse liver extracts. Biochem. 5:1089-1098.

Ganther HE. 1968. Selenotrisulfides. Formation by the reaction of thiols with selenious acid. Biochem. 7:2898-2905.

Ganther HE. 1971. Selenium: the biological effects of a highly active trace substance. In: D. D. Hemphill ed. 1970. Trace substances in environmental health. Univ. of Missouri, Columbia. p. 211.

Ganther HE. Baumann CA. 1962. Selenium metabolism. I. Effects of diet, arsenic and cadmium. J. Nutr. 77:210-220.

Ganther HE, Goudie C, Sunde ML, et al. 1972. Selenium: relation to decreased toxicity of methylmercury added to diets containing tuna. Science 175:1122-1124.

Ganther HE, Hafeman DG, Lawrence RA, Sarfass RE, Hoekstra WG. 1976. Selenium and glutathione peroxidase in health and disease-a review. In: A.S. Prasad. ed. Trace elements in human health and disease. Vol. II. Academic Press, New York. p. 165.

Gissel-Nielsen, G. 1977. Control of selenium in plants. Agricultural Department. Riso National Laboratory, Roskilde. 1-27.

Glover JR. 1970. Selenium and its industrial toxicology. Ind. Med. Surg. 39:26-30.

Grasso P, Abraham R, Hendy R, Diplock AT, Golberg L, Green J. 1969. The role of dietary silver in the production of liver necrosis in vitamin E deficient rats. Exp. Mol. Pathol. 11:186-199.

Greathouse DG. U.S. Environmental Protection Agency. Undated draft health effects summary document on selenium.

Griffin AC. 1979. Role of selenium in the chemoprevention of cancer. Adv. Cancer. Res. 29:419-42.

Griffin AC, Jacobs MM. 1977. Effects of selenium on azo dye hepatocarcinogenesis. Cancer Lett. 3:177-181.

Gross S. 1976. Hemolytic anemia in premature infants: relationship to vitamin E, selenium, glutathione peroxidase, and erythrocyte lipids. Semin. Hematolo. 13:187-199.

Gruenwald P. 1958. Malformation caused by necrosis in the embryo. Illustrated by the effect of selenium compounds on chick embryro. Am. J. Pathol. 34:77-103.

Hadjimarkos DM. 1965. Effect of selenium on dental caries. Arch. Environ. Health. 10:893-899.

Hadjimarkos DM. 1970. Selenium. Lancet 1:721.

Hadjimarkos DM, Bonhorst CW, Mattice JJ. 1959. The selenium concentration in placental tissue and fetal cord blood. J. Pediatr. 54:296-298.

Halverson AW, Guss PL, Olson OE. 1962. Effect of sulfur salts on selenium poisoning in the rat. J. Nutr. 77:459-464.

Halverson AW, Jerde LG, Hills CL. 1965. Toxicity of inorganic selenium salts to chick embryos. Toxicol. Appl. Pharmacol. 7:675-679.

Halverson AW, Monty KJ. 1960. An effect of dietary sulfate on selenium poisoning in the rat. J. Nutr. 70:100-102.

Halverson AW, Palmer IS, Guss PL. 1966. Toxicity of selenium to post-weanling rats. Toxicol. Appl. Pharmacol. 9:477-484.

Hamilton A. 1925. Industrial poisons in the United States. Macmillan Co, New York. pp. 303-304.

Handreck KA, Godwin KD. 1970. Distribution in the sheep of selenium derived from ^{75}Se-labelled ruminal pellets. Aust. J. Agric. Res. 21:71-84.

Hansson E, Jacobsson SO. 1966. Uptake of [^{75}Se] selenomethionine in the tissues of the mouse studied by whole-body autoradiography. Biochem. Biophys. Acta. 115:285-293.

Harbach PR, Swenberg JA. 1981. Effects of selenium on 1,2-dimethylhydrazine metabolism and DNA alkylation. Carcinogenesis 2:575-580.

Harr JR, Bone JF, Tinsley IJ, Weswig PH, Yamamoto RS. 1967. Selenium toxicity in rats. II. Histopathology. In: Muth OH, Oldfield JE, Weswig PH. eds. Selenium in biomedicine. Proc. of 1st Int. Symp., Oregon State University, 1966. AVI Publishing Co., Westport, Conn. p. 153-178.

Harr JR, Exon JH, Weswig PH, Whanger PD. 1973. Relationship of dietary selenium concentration; chemical cancer induction; and tissue concentration of selenium in rats. Clin. Toxicol. 6:487-495.

Harr JR, Exon JH, Whanger PD, Weswig PH. 1972. Effect of dietary selenium on N-2-fluorenyl-acetamide (FAA)-induced cancer in vitamin E supplemented, selenium depleted rats. Clin. Toxicol. 5:187-194.

Harr JR, Muth OH. 1972. Selenium poisoning in domestic animals and its relationship to man. Clin. Toxicol. 5:175-186.

Hauskneckt D, Ziskind R. 1976. Health effects of selenium. Science Applications, Inc. p. 3. EPRI 571-1.

Heit M. 1977. A review of current information on some ecological and health related aspects of the release of trace metals into the environment associated with the combustion of coal. New York: U.S. Energy Research and Development Administration.

Hoekstra WG. 1975. Biochemical function of selenium and its relation to vitamin E. Fed. Proc. 34:2083-2089.

Hogue DE, Proctor JF, Warner RC, Loosli JK. 1962. Relation of selenium vitamin E and an unidentified factor to muscular dystrophy (stiff-lamb or white muscle disease) in the lamb. J. Animal Sci. 21:25-29.

Holmberg RE Jr., Ferm VH. 1969. Interrelationships of selenium, cadmium, and arsenic in mammalian teratogenesis. Arch. Environ. Health 18:873.

Hopkins LL Jr., Majaj AS. 1967. Selenium in human nutrition. In: O.H. Muth, J.E. Oldfield and P.H. Weswig, eds. Selenium in biomedicine. AVI Publishing Co., Westport, Conn. p. 203-214.

IARC. 1975. International Agency for Research in Cancer. Evaluation of carcinogenic risk of chemicals to man. Monogr. No. 9 Lyon, France. pp. 245-260.

ICRP. 1975. International Commission on Radiological Protection. Report of the task group on reference man. New York: Pergamon Press.

Iijima S, Tohyama C, Lu C, Matsumoto N. 1978. Placental transfer and body distribution of methylmercury and selenium in pregnant mice. Toxicol. Appl. Pharmacol. 44:143-146.

Jacobs MM. 1977. Inhibitory effects of selenium on 1,2-dimethylhydrazine and methylaroxymethanol colon carcinogenesis. Correlative studies on selenium effects on the mutagenicity and sister chromatid exchange rates of selected carcinogens. Cancer 40:2557-2564.

Jacobs MM, Jansson B, Griffin AC. 1977a. Inhibitory effects of selenium on 1,2-dimethylhydrazine and methylazoxymethanol acetate induction of colon tumors. Cancer Lett. 2:133-138.

Jacobs MM, Matney TS, Griffin AC. 1977b. Inhibitory effects of selenium on the mutagenicity of 2-acetylaminofluorene (AAF) and AAF derivatives. Cancer Lett. 2:319-322.

Jacobson S, Wester PO. 1977. Balance study of twenty trace elements during total parenteral nutrition in man. Brit. J. Nutr. 37:107-126.

Jansson B, Jacobs MM, Griffin AC. 1978. Gastrointestinal cancer: epidemiology and experimental studies. Adv. Exp. Med. Biol. 91:305-22.

Johnson RA, Baker SS, Fallon JT, Maynard EP, Ruskin JN, Wen Z, Ge K, Cohen HJ. 1981. An occidental case of cardiomyopathy and selenium deficiency. NEJM 304:1210-1212.

Kar AB, Das RP, Mukerji B. 1960. Prevention of cadmium-induced changes in the gonads of rat by zinc and selenium: a study in the antagonism between metals in the biological system. Proc. Natl. Inst. Sci. India part B, Suppl. 26.

Keshan Disease Research Group. 1979a. Observations on effect of sodium selenite in prevention of Keshan disease. Chinese Med. J. 92:471-476.

Keshan Disease Research Group. 1979b. Epidemiologic studies on the etiologic relationship of selenium and Keshan disease. Chinese Med. J. 92:477-482.

Kilness AW, Hochberg FH. 1977. Amyotrophic lateral sclerosis in a high selenium environment. JAMA 237:2843-2844.

Kincaid RL, Miller WJ, Neathery MW, Gentry RP, Hampton DL. 1977. Effect of added dietary selenium on metabolism and tissue distribution of radioactive and stable selenium in calves. J. Anim. Sci. 44:147-157.

Klewska A. 1978. Physiological levels of selenium in biological material. Arch. Med. Sadowej Kryminol. 28:307-312. (In Polish; summary in English)

Klug HL, Petersen DF, Moxon AL. 1949. The toxicity of selenium analogues of cystine and methionine. Proc. S. Dak. Acad. Sci. 28:117.

Koller LD, Isaacson-Kerkvliet N, Exon JH, et al. 1979. Synergism of methylmercury and selenium producing enhanced antibody formation in mice. Arch. Environ. Health 34:248-252.

Koller LD, South PJ, Exon JH, Whitbeck GA. 1983. Selenium deficiency of beef cattle in Idaho and Washington and a practical means of prevention. The Cornell Vet. 73:323-332.

Kolm KE. 1975. Selenium in soils of the lower Wasatch formation, Campbell County, Wyoming: geochemistry, distribution, and environmental hazards. Wyoming Univ. Dept. of Geology, Laramie. p. 24.

Konz J. 1979. A preliminary assessment of selenium in drinking water. Prepared by Mitre Corporation for Office of Drinking Water, U.S. Environmental Protection Agency, Washington, DC. EPA-570/9-79-012.

Landauer W. 1950. Studies on the creeper fowl. XIII. The effect of selenium and the asymmetry of selenium-induced malformations. J. Exp. Zool. 83:431-443.

Latshaw JD. 1975. Natural and selenite selenium in the hen and egg. J. Nutr. 105:32-37

Lee M, Chan KK, Sairenji E, Nhkuni T. 1979. Effect of sodium selenite on methylmercury-induced cleft palate in the mouse. Environ. Res. 19:39-48.

Lemley RE. 1940. Selenium poisoning in the human. Lancet 60:528-531.

Lemley RE, Merryman MP. 1941. Selenium poisoning in the human. Lancet. 61:435-438.

Letkiewicz F, Spooner C, Macaluso C, Borum D. 1984. Occurrence of selenium in drinking water, food, and air. Prepared by JRB Associates, McLean, VA, for Office of Drinking Water U.S. Environmental Protection Agency.

Levander OA. 1976. Selenium in foods. In: Proceedings of the Symposium on Selenium and Tellurium in the Environment. Ind. Health Foundation, Inc., Pittsburgh, Penn. p. 26-53.

Levander OA. 1972. Metabolic interrelationships and adaptations in selenium toxicity. Ann. N.Y. Acad. Sci. 192:181-192.

Levander OA, Argrett LC. 1969. Effects of arsenic, mercury, thallium, and lead on selenium metabolism in rats. Toxicol. Appl. Pharmacol. 14:308-314.

Levander OA, Baumann CA. 1966. Selenium metabolism. VI. Effect of arsenic on the excretion of selenium in the bile. Toxicol. Appl. Pharmacol. 9:106-115.

Levander OA, Morris VC. 1970. Interactions of methionine, vitamin E, and antioxidants in selenium toxicity in the rat. J. Nutr. 100:1111-1118.

Lipmann F. 1958. Biological sulfate activation and transfer. Science 128:575-581.

Lo LW, Koropatnick J, Stich HF. 1978. The mutagenicity and cytotoxicity of selenite, "activated" selenite and selenate for normal and DNA repair-deficient human fibroblasts. Mutat. Res. 49:305-12.

Maag DD, Orsborn JS, Clopton JR. 1960. The effect of sodium selenite on cattle. Am. J. Vet. Res. 21:1049-1053.

Magat W, Sell JL. 1979. Distribution of mercury and selenium in egg components and egg-white proteins. Proc. Soc. Exp. Biol. Med. 161:458-63.

Mahan DC, Moxon AL, Hubbard M. 1977. Efficacy of inorganic selenium supplementation to sow diets on resulting carry-over to their progeny. J. Anim. Sci. 46:738-46.

Marshall MV, Arnott MS, Jacobs MM, Griffin AC. 1979. Selenium effects on the carcinogenicity and metabolism of 2-acetylaminofluorene. Cancer Lett. 7:331-338.

Mason KE, Young JO. 1967. Effectiveness of selenium and zinc in protecting against cadmium-induced injury of the rat testis. In: Muth OH, Oldfield JE, Weswig PH, eds. Symposium: selenium in biomedicine. AVI Publishing Co., Inc., Westport, Connecticut. p. 383-394.

McConnell KP, Broghamer WL, Blotcky AJ, Hurt OJ. 1975. Selenium levels in human blood and tissue in health and disease. J. Nutr. 105:1026-1031.

McConnell KP, Jager RM, Bland KI, Blotcky AJ. 1980. The relationship of dietary selenium and breast cancer. J. Surg. Oncol. 15:67-70.

McKeehan WL, Hamilton WG, Ham RG. 1976. Selenium is an essential trace nutrient for growth of WI-38 diploid human fibroblasts. Proc. Natl. Acad. Sci. 73:2023-2027.

McKenzie JM, Rea HM, Van Rij AM, Robinson MF. 1976. Low blood selenium concentrations during intravenous alimentation. Proc. Univ. Otago Med. School, New Zealand. 54:25.

Medina D, Lane H, Shepard F. 1981. Effects of selenium on mouse mammary tumorigenesis and glutathione peroxidase activity. Anticancer Res. 1:377-382.

Medina D, Shepard F. 1981. Selenium-mediated inhibition of 7,12-dimethylbenz [a] anthracene-induced mouse mammary tumorigenesis. Carcinogenesis 2:451-455.

Millar KR, Sheppard AD. 1972. a-Tocopherol and selenium levels in human and cow's milk. New Zealand J. Sci. 15:3-15.

Miller WT, Williams KT. 1940. Minimum lethal dose of selenium as sodium selenite for horses, mules, cattle and swine. J. Agr. Res. 60:153-173.

Money DFL. 1970. Vitamin E and selenium deficiencies and their possible aetiological role in sudden death in infants syndrome. New Zealand Med. J. 71:32-34.

Moxon AL. 1938. The effect of arsenic on the toxicity of seleniferous grains. Science 88:81.

Moxon AL, Dubois KP. 1939. The influence of arsenic and certain other elements on the toxicity of seleniferous grains. J. Nutr. 18:447.

Moxon AL, Rhian MA. 1943. Selenium poisoning. Physiol. Rev. 23:305-337.

Moxon AL, Jensen CW, Paynter CR. 1947. The influence of germanium, gallium, antimony, and some organic arsenicals on the toxicity of selenium. Proc. S. Dak. Acad. Sci. 26:21-26.

Moxon AL, Paynter CR, Halverson AW. 1945. Effect of route of administration on detoxication of selenium by arsenic. J. Pharmacol, Exp. Ther. 84:115-119.

Moxon AL, Rhian MA, Anderson HD, Olson OE. 1944. Growth of steers on seleniferous range. J. Anim. Sci. 3:299-309.

Munsell HE, DeVaney GM, Kennedy MH. 1936. Toxicity of food containing selenium as shown by its effect on the rat. U.S. Dept. Agr. Tech. Bull. No. 534:1-25.

Muth OH, Oldfield JE, Remmert LF, Schubert JR. 1958. Effects of selenium and vitamin E on white muscle disease. Science 128:1090.

Muth OH, Weswig PH, Whanger PD, Oldfield JE. 1971. Effect of feeding selenium-deficient ration to the subhuman primate (Saemiri sciureus). Am. J. Vet. Res. 32:1603-1605.

Nakamuro K, Yoshikawa K, Sayato Y, Kurata H, Tonomura M, Tonomura A. 1976. Studies on selenium-related compounds. V. Cytogenetic effect and reactivity with INA. Mutat. Res. 40:177-184.

NAS. 1971. National Academy of Sciences. Comm. on Anim. Nutr. Selenium in Nutrition. Washington, D.C.

NAS. 1976. National Academy of Sciences. Selenium. Comm. Med. Biol. Effects, Environ. Pollut. Subcomm. Selenium. Washington, D.C.

NAS. 1977. National Academy of Sciences. Drinking water and health. Washington, D.C. p. 344-368.

NAS. 1980a. National Academy of Sciences. Drinking water and health. Volume 3. Washington, DC: National Academy Press pp. 19-61.

NAS. 1980b. National Academy of Sciences, Food and Nutrition Board. Recommended dietary allowances, 9th Rev. Natl. Res. Council, ed. Natl. Acad. Sci., Washington, D.C. p. 162-164.

NCI. 1980. National Cancer Institute. Bioassay of selenium sulfide (gavage) for possible carcinogenicity. NCI Technical Report Series No. 194. NTP No. 80-17.

Nelson AA, Fitzhugh OG, Calvery HO. 1943. Liver tumors following cirrhosis caused by selenium in rats. Cancer Res. 3:230-236.

NIOSH. 1980. National Institute of Occupational Health and Safety. NIOSH/OSHA standards completion program: Draft technical standard and supporting document for selenium compounds.

Nishioka, H. 1972. Mutagenic activities of metal compounds in bacteria. Mutal. Res. 31:185-189.

Nobunaga TH, Satoh T, Suzuki. 1979. Effects of sodium selenite on methylmercury embryotoxicity and teratogenicity in mice. Toxicol. and Appl. Pharm. 47:79-88.

Noda M, Takano T, Sakurai H. 1979. Mutagenic activity of selenium compounds. Mutat. Res. 66:175-9.

Nugteren DH, Hazelhof E. 1973. Isolation and properties of intermediates in prostaglandin biosynthesis. Biochim. Biophys. Acta. 326:448-461.

Obermeyer BD, Palmer IS, Olson OE, Halverson AW. 1971. Toxicity of trimethylselenonium chloride in the rat with and without arsenite. Toxicol. Appl. Pharmacol. 20:135-146.

Omaye ST, Reddy KA, Cross CE. 1978. Enhanced lung toxicity of paraquat in selenium-deficient rats. Toxicol. Appl. Pharmacol. 43:237-47.

Orstadius K. 1960. Toxicity of a single subcutaneous dose of sodium selenite in pigs. Nature 188:1117.

OSHA. 1978. Occupational Health and Safety Administration. General industry standards. 29CFR 1910.1000. p. 543.

Palmer IS, Arnold RL, Carlson CW. 1973. Toxicity of various selenium derivatives to chick embryos. Poult. Sci. 52:1841-1846.

Palmer IS, Fischer DD, Halverson AW, Olson OE. 1969. Identification of major selenium excretory product in rat urine. Biochim. Biophys. Acta 177:336-342.

Palmer IS, Olson OE. 1974. Relative toxicities of selenite and selenate in the drinking water of rats. J. Nutr. 104:306-314.

Parizek J, Babicky A, Ostadalova I, Kalouskova J, Pavlik L. 1969. The effect of selenium compounds on the cross-placental passage of ^{203}Hg. In: Sikov MR, Mahlum DD. eds. Radiation biology of fetal and juvenile mammals. U.S. AEC, Oak Ridge, Tenn. p. 137-143.

Parizek J, Ostadalova I. 1967. The protective effect of small amounts of selenite in sublimate intoxication. Experientia 23:142-143.

Parizek J, Ostadalova I, Benes I, Babicky A. 1968. Pregnancy and trace elements: the protective effect of compounds of an essential trace element - selenium - against the peculiar toxic effects of cadmium during pregnancy. J. Reprod. Fertil. 16:507-509.

Parizek J, Ostadalova I, Kalouskova J, Babicky A, Benes J. 1971a. The detoxifying effects of selenium. Interrelations between compounds of selenium and certain metals. In: Mertz W, Cornatzer WE. eds. Newer trace elements in nutrition. Marcel Dekker, New York. pp. 85-122.

Parizek J, Ostadalova I, Kalouskova J, Babicky A, Pavlik L, Bibr B. 1971b. Effect of mercuric compounds on the maternal transmission of selenium in the pregnant and lactating rat. J. Reprod. Fert. 25:157-170.

Paton GR, Allison AC. 1972. Chromosome damage in human cell cultures induced by metal salts. Mutat. Res. 16:332-336.

Patrias G, Olson OE. 1969. Selenium contents of samples of corn from Midwestern states. Feedstuffs 41:32.

Pedersen ND, Whanger PD, Weswig PH, Muth OH. 1972. Selenium binding proteins in tissues of normal and selenium responsive myopathic lambs. Bioinorg. Chem. 2:33-45.

Perry TW, Peterson RC, Griffin DD, Beeson WM. 1978. Relationship of blood serum selenium levels of pregnant cows to low dietary intake, and effect on tissue selenium levels of their calves. J. Anim. Sci. 46:562-5.

Poley WE, Moxon AL. 1938. Tolerance levels of seleniferous grains in laying rations. Poult. Sci. 17:72-76.

Poley WE, Moxon AL, Franke KW. 1937. Further studies of the effects of selenium poisoning on hatchability. Poult. Sci. 16:219-225.

Rabar I, Kostial K. 1981. Bioavailability of cadmium in rats fed various diets. Arch. Toxicol. 47:63-66.

Ray JH, Altenburg LC. 1978. Sister-chromatid exchange induction by sodium selenite: dependence on the presence of red blood cells or red blood cell lysate. Mutat. Res. 54:343-54.

Ray JH, Altenburg LC. 1980. Dependence of the sister-chromatid exchange-inducing abilities of inorganic selenium compounds on the valence state of selenium. Mutat. Res. 78:261-266.

Ray JH, Altenburg LC, Jacobs MM. 1978. Effect of sodium selenite and methyl methanesulfonate or N-hydroxy-2-acetyl-aminofluorene co-exposure on sister-chromatid exchange production in human whole blood cultures. Mutat. Res. 57:359-368.

Rea HM, Thomson CD, Campbell DR, Robinson MF. 1979. Relation between erythrocyte selenium concentrations and glutathione peroxidase (EC 1.11.1.9) activities of New Zealand residents and visitors to New Zealand. Br. J. Nutr. 42:201-8.

Rhead WJ, Schrauzer GN, Saltzstein SL. 1973. Sudden death in infancy and vitamin E deficiency. Brit. Med. J. 4:548.

Rhead WJ, Schrauzer GN, Saltzstein SL, Cary EE, Allaway WH. 1972. Vitamin E, selenium and the sudden death syndrome. J. Pediatr. 81:415-416.

Ridgway LP, Karnofsky DA. 1952. The effects of metals on the chick embryo: toxicity and production of abnormalities in development. Ann N.Y. Acad. Sci. 55:203-215.

Robertson DSF. 1970. Selenium, a possible teratogen? Lancet 1:518-519.

Rosenfeld I. 1964. Excretion and retention of ^{75}Se in relation to modes of administration, toxicity, and pregnancy in rats. Metabolic effects and metabolism of selenium in animals. Part IV, Bull. 414. Agric. Exp. Sta., University of Wyoming. pp. 35-52.

Rosenfeld I, Beath OA. 1947. Congenital malformations of eyes of sheep. J. Agr. Res. 75:93-103.

Rosenfeld I, Beath OA. 1954. Effect of selenium on reproduction in rats. Proc. Soc. Exptl. Biol. Med. 87:295-297.

Rosenfeld I, Beath OA. 1964. Selenium: geobotany, biochemistry, toxicity and nutrition. Academic Press, New York. p. 288.

Rotruck JT, Pope AL, Ganther HE, et al. 1973. Selenium: biochemical role as a component of glutathione peroxidase. Science 179:588-590.

Rudolph N, Wong SL. 1978. Selenium and glutathione peroxidase activity in maternal and cord plasma and red cells. Pediatr. Res. 12:789-92.

Rusiecki W, Brzezinski J. 1966. Influence of sodium selenate on acute thallium poisonings. Acta Pol. Pharmacol. 23:74-80.

Schrauzer GN, Ishmael D. 1974. Effects of selenium and of arsenic on the genesis of spontaneous mammary tumors in inbred C_3H mice. Ann. Clin. Lab. Sci. 4: 441-447.

Schrauzer GN, Rhead WJ. 1971. Interpretation of the methylene blue reduction test of human plasma and the possible cancer protecting effect of selenium. Experientia 27:1069-1071.

Schrauzer GN, White DA, Schneider CJ. 1976. Inhibition of genesis of spontaneous mammary turmors in C3H mice-effects of selenium and of selenium-antagonistic elements and their possible role in human breast cancer. Bioinorg. Chem. 6:265.

Schrauzer GN, White DA, Schneider CJ. 1978. Selenium and cancer: effects of selenium and of the diet on the genesis of spontaneous mammary tumors in virgin inbred female C3H/ST mice. Bioinorg. Chem. 8:387-96.

Schroeder HA. 1967. Effects of selenate, selenite, and tellurite on the growth and early survival of mice and rats. J. Nutr. 92:334.

Schroeder HA, Mitchener M. 1971a. Selenium and tellurium in rats: effect on growth, survival and tumors. J. Nutr. 101:1531.

Schroeder HA, Mitchener M. 1971b. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health 23:102-106.

Schroeder HA, Mitchener M. 1972. Selenium and tellurium in mice: effects on growth, survival and tumors. Arch. Environ. Health 24:66-71.

Schroeder HA, Frost DV, Balassa JJ. 1970. Essential trace metals in man: Selenium. J. Chron. Dis. 23:227-243.

Schut HAJ, Thorgeirsson SS. 1979. Mutagenic activation of N-hydroxy-2-acetylaminofluorene by developing epithelial cells of rat small intestine and effects of antioxidants. J. Natl. Cancer Inst. 63:1405-1409.

Schwarz K. 1961. Development and status of experimental work on Factor 3 selenium. Fed. of American Soc. for Exp. Biol: 20:666-673.

Schwarz K. 1951a. A hitherto unrecognized factor against dietary necrotic liver degeneration, in American Yeast (factor 3). Proc. Soc. Exp. Biol. Med. 78:852-856.

Schwarz K. 1951b. Production of dietary necrotic liver degeneration using American Torula yeast. Proc. Soc. Exp. Biol. Med. 77:818-823.

Schwarz K. 1954. Factor protecting against dietary necrotic liver degeneration. Ann. N.Y. Acd. Sci. 57:878-888.

Scott ML. 1973. The selenium dilemma. J. Nutr. 103:803-810.

Scott ML. 1976. Selenium and tellurium - environmental health aspects. Proceedings of the Symposium on Selenium-Tellurium in the Environment. Industrial Health Foundation, Inc., Pittsburgh, Penn. pp. 341-342.

Scott ML. 1979. Vitamin E and selenium: solution of a long term enigma. Am. Nutr. Health Aug.-Sept. 26-29.

Sell JL. 1977. Comparative effects of selenium on metabolism of methylmercury by chickens and quail: tissue distribution and transfer into eggs. Poult. Sci. 56:939-948.

Sentein P. 1967. Actions de derives du selenium (seleniates et selenites) comparee a celle d'acides divers sur les mitoses de segmentation. Chromasoma 23:95-136. (In French; English abstract).

Serfass RE, Ganther HE. 1975. Defective microbicidal activity in glutathione peroxidase-deficient neutrophils of selenium-deficient rats. Nature 255:640-641.

Shacklette H, Boernger JG, Keith JR. 1974. Selenium, fluorine and arsenic in surficial materials of the conterminous United States, Geologic Survey Circular 692. p. 1-14.

Shamberger RJ. 1970. Relationship of selenium to cancer. I. Inhibitory effect of selenium on carcinogenesis. J. Nat. Cancer Inst. 44:931-936.

Shamberger RJ. 1971. Is selenium a teratogen? Lancet 2:1316.

Shamberger RJ. 1976. Selenium in health and disease. Proceedings of the Symposium on Selenium-Tellurium in the Environment, Industrial Health Foundation, Inc., Pittsburgh, Penn. pp. 253-267.

Shamberger RJ, Corlett CL, Beaman KD, Kasten BL. 1979. Antioxidants reduce the mutagenic effect of malonaldehyde and b-propiolactone. Part IX. Antioxidants and cancer. Mutat. Res. 66:349-355.

Shamberger RJ, Frost DV. 1969. Possible protective effect of selenium against human cancer. Can. Med. Assoc. J. 100:682.

Shamberger RJ, Rukovena E, Longfield AK, et al. 1973. Antioxidants and cancer. I. Selenium in the blood of normals and cancer patients. J. Natl. Cancer Inst. 50:863-870.

Shamberger RJ, Tytko SA, Willis CE. 1975. Selenium and heart disease. IX. Trace substances in environmental health. D.D. Hemphill, ed. Univ. Missouri Press, Columbia, MO. pp. 15-22.

Shamberger RJ, Willis CE. 1971. Selenium distribution and human cancer mortality. Crit. Rev. Clin. Lab. Sci. 2:211.

Shapiro JR. 1973. Selenium compounds in nature and medicine: selenium and human biology. In: Klayman DL, Guenther WHH, eds. Organic selenium compounds: their chemistry and biology. John Wiley and Sons, New York. pp. 694-725.

Shearer TR, Hadjimarkos DM. 1975. Geographic distribution of selenium in human milk. Arch. Environ. Health. 30:230-233.

Shukla VKS, Jensen GE, Clausen J. 1977. Erythrocyte glutathione peroxidase deficiency in multiple sclerosis. Acta Neurol. Scand. 56:542.

Smith MI, Franke KW, Westfall BB. 1936. The selenium problem in relation to public health. A preliminary survey to determine the possibility of selenium intoxication in the rural population living on seleniferous soil. U.S. Pub. Health Rep. 51:1496-1505.

Smith MI, Stohlman EF, Lillie RD. 1937. The toxicity and pathology of selenium. J. Pharmacol. Exp. Ther. 60:449-471.

Smith MI, Westfall BB. 1937. Further field studies on the selenium problem in relation to public health. U.S. Pub. Health Rep. 52:1375-1384.

Soullier BK, Wilson PS, Nigro ND. 1981. Effect of selenium on azoxymethane-induced intestinal cancer in rats fed high fat diet. Cancer Lett. 12:343-348.

Spallholz JE, Martin JL, Gerlach ML, Heinzerling RH. 1975. Injectable selenium: effect on the primary immune response of mice. Proc. Soc. Exp. Biol. Med. 148:37-40.

Stadtman TC. 1979. Some selenium-dependent biochemical processes. In: Meister A., ed. Advances in enzymology and related areas of molecular biology. John Wiley & Sons, New York. pp. 1-28.

Stadtman TC. 1974. Selenium biochemistry. Proteins containing selenium are essential components of certain bacterial and mammalian enzyme systems. Science. 183:915-921.

Stewart RD, Griffiths NM, Thomson CD, Robinson MF. 1978. Quantitative selenium metabolism in normal New Zealand women. Br. J. Nutr. 40:45-54.

Sundberg S, Luuka P, Andersen K, Eriksson AW, Siltanen P. 1975. Blood pressure in adult Lapps and Skolts. Ann. Clin. Res. 7:17-22.

Sunde RA, Hoekstra WG. 1980. Structure, synthesis and function of glutathione peroxidase. Nutr. Rev. 38:265-273.

Tank G, Storvick CA. 1960. Effect of naturally occurring selenium and vanadium on dental caries. J. Dent. Res. 39:473-488.

Tappel AL. 1962. Vitamin E as the biological lipid antioxidant. Vitam. Horm. 20:493-510.

Thapar NT, Guenthner E, Carlson CW, Olson OE. 1969. Dietary selenium and arsenic additions to diets for chickens over a life cycle. Poult. Sci. 48:1988-1993.

Thompson HJ, Becci PJ. 1979. Effect of graded dietary levels of selenium on tracheal carcinomas induced by 1-methyl-1-nitrosourea. Cancer Lett. 7:215-9.

Thompson HJ, Becci PJ. 1980. Selenium inhibition of N-methyl-N-nitrosourea-induced mammary carcinogenesis in the rat. JNCI 65:1299-1301.

Thompson JN, Scott ML. 1970. Impaired lipid and vitamin E absorption related to atrophy of the pancreas in selenium-deficient chicks. J. Nutr. 100:797-809.

Thomson CD. 1972. Urinary excretion of selenium in some New Zealand women. Proc. Univ. Otago Med. School, New Zealand. 50:31-32.

Thomson CD, Rea HM, Chapman OW, Robinson MF. 1977. Low blood selenium concentrations and glutathione peroxidase activities in elderly people. Proc. Univ. Otago Med. School. 55:18-19.

Thomson CD, Robinson BA, Stewart RDH, Robinson MF. 1975. Metabolic studies of [^{75}Se] selenocystine and [^{75}Se] selenomethionine in the rat. Br. J. Nutr. 34:501-509.

Thomson CD, Robinson MF. 1980. Selenium in human health and disease with emphasis on those aspects peculiar to New Zealand. Am. J. Clin. Nutr. . 33:303-23.

Thomson CD, Stewart RDH. 1973. Metabolic studies of [^{75}Se] selenomethionine and [^{75}Se] selenite in the rat. Br. J. Nutr. 30:139-147.

Thomson CD, Stewart RDH. 1974. The metabolism of [^{75}Se] selenite in young women. Br. J. Nutr. 32:47-57.

Ting KP, Walker GWR. 1969. The distributive effect of selenoamino acid treatment on crossing-over in Drosophila melanogaster. Genetics 61:141-155.

Tinsley IJ, Harr JR, Bone JF, Weswig PH, Yamamoto RS. 1967. Selenium toxicity in rats. I. Growth and longevity. In: Muth OH, Oldfield OE, Weswig PH, eds. Selenium in biomedicine. First International Symposium, Oregon State University. AVI Publishing Co., Westport, Connecticut. p. 141-152.

Tsongas TA, Ferguson SW. 1977. Human health effects of selenium in a rural Colorado drinking water supply. Presented at Trace Substances in Env. Health, 11th Conf., University of Missouri, Columbia. p. 30-35.

Tsongas TA, Ferguson SW. 1978. Selenium concentrations in human urine and drinking water. In: Kirchgessner M, ed. Trace element metabolism in man and animals. 3rd International Symposium Proceedings. Freising- Weihenstephen, Germany. p. 320-321.

Underwood EJ. 1977. Trace elements in human and animal nutrition, 4th ed. New York, NY: Academic Press pp. 302-346.

USBM. 1980. United States Bureau of Mines. Minerals yearbook, 1978-1979. Vol. 1. U. S. Department of the Interiors. Bureau of Mines, Washington, D.C. p. 1043-1046.

USEPA. 1974. United States Environmental Protection Agency. Safe drinking water act, public law 93-523, 93rd Congress. p. 1661.

USEPA. 1976. United States Environmental Protection Agency. National Interim primary drinking water regulations. EPA 570/9-76-003.

USEPA. 1980. United States Environmental Protection Agency. Ambient water quality criteria for selenium. EPA-440/5-80-070.

USPHS. 1962. U.S. Public Health Service. Drinking water standards. U.S. Dept. of Health, Education and Welfare. Publ. No. 956. p. 52.

Valentine JL, Kang HK, Spivey GH. 1978. Selenium levels in human blood, urine, and hair in response to exposure via drinking water. Env. Res. 17:347-355.

Van Rij AM, Thomson CD, McKenzie JM, Robinson, MF. 1979. Selenium deficiency in total parenteral nutrition. Am. J. Clin. Nutr. 32:2076-2085.

Van Vleet JF. 1980. Current knowledge of selenium-vitamin E deficiency in domestic animals. JAVMA 176:321-325.

Van Vleet JF, Ferrans VJ, Ruth GR. 1977. Ultrastructural alterations in nutritional cardiomyopathy of selenium-vitamin E deficient swine. I. Fiber lesions. Lab. Invest. 37:188-200.

Venugopal B, Luckey TD. 1977. Metal toxicity in mammals. Plenum Press, New York. p. 244.

Volgarev MN, Tscherkes LA. 1967. Further studies in tissue changes associated with sodium selenate. In: Muth OH, Oldfield JE, Weswig PH, eds. Selenium in biomedicine. 1st International Symposium, Oregon State University. AVI Publishing Co., Westport, Connecticut. p.179-184.

Wahlstrom RC, Olson OE. 1959. The effect of selenium on reproduction in swine. J. Animal Sci. 18:141-145.

Waterlow JC, Garrow JS, Millward OJ. 1969. The turnover of [^{75}Se] selenomethionine in infants and rats measured in a whole body counter. Clin. Sci. 36:489-504.

Watkinson JH. 1974. The selenium status of New Zealanders. New Zealand Med. J. 80:202-205.

Weast RC, Astle MJ. 1979. Handbook of chemistry and physics. 60th ed. CRC Press, Inc., Boca Raton. p. B-20-21.

Westermarck T. 1977. Selenium content of tissues in Finnish infants and adults with various diseases, and studies on the effects of selenium supplementation in neuronal ceroid lipofuscinosis patients. Acta Pharmacol. Toxicol. 41:121-8.

Westermarck T, Raunu P, Kirjarinta M, Lappalainen L. 1977. Selenium content of whole blood and serum in adults and children of different ages from different parts of Finland. Acta. Pharmacol. Toxicol. 40:465-475.

Westermarck T, Sandholm M. 1977. Decreased erythrocyte glutathione peroxidase activity in neuronal ceroid lipofuscinosis (NCL)-corrected with selenium supplementation. Acta Pharmacol. Toxicol. 40:70-74.

Whiting RF, Wei L, Stich HF. 1980. Unscheduled DNA synthesis and chromosome aberrations induced by inorganic and organic selenium compounds in the presence of glutathione. Mutat. Res. 78:159-69.

WHO. 1980. World Health Organization. Guidelines for drinking water quality-health-related inorganic constituents. Background documentation from Inorganics Task Group. Copenhagen, September 22-26, 1980.

Wilber CG. 1980. Toxicology of selenium: a review. Clin. Toxicol. 17:171-230.

Willett WC, Morris JC, Pressel S et al. 1983. Prediagnostic serum selenium and risk of cancer. Lancet 16:130-133.

Wilson LG, Bandurski RS. 1956. An enzymatic reaction involving adenosine triphosphate and selenate. Arch. Biochem. Biosphys. 62:503-506.

Windholz M, ed. 1976. The Merck index. 9th ed. Merck and Co. Inc., Rahway, New Jersey. p. 1091-93.

Witting LA, Horwitt MK. 1964. Effects of dietary selenium, methionine, fat level, and tocopherol on rat growth. J. Nutr. 84:351-357.

Yang G, Wang S, Zhou R, Sun S. 1983. Endemic selenium intoxication of humans in China. American J. Clin. Nutr. 37:872-881.

Zabel NL, Harland J, Gormican AT, Ganther HE. 1978. Selenium content of commercial formula diets. Am. J. Clin. Nutr. 31:850-858.